AUSTRALIAN Biotechnology NEWS

From laboratory to bedside

FIONA WYLIE, AUSTRALIAN LIFE SCIENTIST

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"It is not that stem cell transplantation doesn't work, it is just that we need more work to figure it out." With this kind of simple optimism, and a little green jasmine tea, Professor Brent Reynolds chatted with Fiona Wylie about life, coincidence and the use of neural stem cells to treat spinal cord injury.

Brian Reynolds is one of a distinguished list of speakers making up a two-part session, "In the search for a cure for spinal cord injury - from laboratory to bedside", at the Australian Health & Medical Research Congress (AH&MRC) at the Melbourne Convention Centre from November 26 to December 1.

Reynolds moved from Canada to the Queensland Brain Institute (QBI) at the University of Queensland in 2004. His path to this point has been somewhat unorthodox to say the least, particularly for someone who published a Science paper and devised an important new tool for the entire field during his PhD.

Immediately after finishing his doctorate in 1994, Reynolds founded a company called NeuroSpheres, based on this new technology.

"I was the director of research and we worked with large pharma and several biotechnology companies to further develop and protect the technology," Reynolds says. "Today NeuroSphere transplantation technology is licensed to Stem Cell Inc, based in California, who are about to start clinical trials based on technology we developed and patented, which is kind of exciting."

Impressively, the technology is also the basis of Phase II trials by another company for treating stroke, and at least half a dozen clinical trials starting in 2007-2008.

The unorthodox route to the QBI began in 1997, when Reynolds opted out of science to study Chinese medicine. He and his family spent the next few years between Thailand, running a yoga centre, and Salt Spring Island off the west coast of Canada, where Reynolds had a Chinese medicine clinic.

The lure back to science came in 2002 when an old university friend in Vancouver, who was head of business development with a company called StemCell Technologies, contacted him because the company wanted to get into the neural stem cell field.

"Things weren't working, he heard that I had moved to the west coast so he asked if I

would come and have a look at this stuff, and I started going to help him one day a week," Reynolds says. "It was also near a really good yoga teacher."

To help out, Reynolds got on the phone to former contacts looking for technology to license. One of these wa Rietze, who used to work with Reynolds at NeuroSpheres. Rietze had just moved from Melbourne up to Que with Professor Perry Bartlett to set up the QBI.

It seems the next step was meant to be - Reynolds and his family had just been convinced by a friend from Tl that Australia, and particularly Brisbane, was a great place to live.

"So Rod arrives and is telling me all about this new institute and says I should come and work with them in Br it was perfect."

Neural stem cells

Since his arrival in the Sunshine State, Reynolds and his team at the QBI have been developing methodolog be patented) to identify and expand distinct cell populations within a heterogeneous milieu of neural stem cell culture to benefit transplantation therapies, in particular spinal cord injury.

"The existence of stem cells in the adult mammalian central nervous system (CNS) and our ability to isolate a expand them ex vivo provides a number of therapeutic opportunities when it comes to treating spinal cord inju Reynolds says.

Cell transplants into nervous tissue have been going on in animal models now for two to three decades. Prim of the work has been done in rodent models of Parkinson' disease, with over 1000 reported studies of transpl into the brain. Human studies have also been carried out, with 300 to 400 people receiving human foetal tissu

Basically, there were lots of promising results, and some not so promising results. Reynolds uses this historic to highlight the two main problems with neural cell transplantation, which he will discuss along with ways to sc problems at the AH&MRC.

Firstly, there is never going to be enough primary foetal tissue available for transplants, especially given the e moral issues to be considered, he says. The primary requirement in this field is therefore a renewable source stem cells.

One possibility is embryonic stem (ES) cells, differentiated down the neural lineage and grown up in culture fc transplants. The problem with ES cells is that they are undifferentiated cells to start with and there is a chanc only slight, that one of those cells doesn't terminally differentiate and grows to form a tumour after transplanta

"All you are going to need is one tumour in one patient, and it will kill the whole field," he says. "That is what h in the late '90s with gene therapy."

This issue is highlighted by a paper just published in Nature Medicine showing that human ES cells differentia dopamine neurons and transplanted into a rodent model of Parkinson's cured the symptoms of the disease. A animals, however, developed tumours. The solution is better ways to sort cell populations early on in the piec Reynolds' group is also working on assays to do this.

The other possible renewable source are neural stem cells grown as neurospheres, which are clusters of cell tissue culture from primary neural stem cells isolated from either adult or foetal tissue. These neurospheres c grown up in large quantities in vitro for transplantation into patients.

As mentioned, Reynolds actually developed the neurosphere assay (NSA), which is now widely used to isolat propagate and enumerate stem cells derived from the CNS. It is now recognised, however, that not all the neurospheres in a culture are derived from stem cells as first thought. About 90 per cent come from progenitc the numbers of stem cells represented by the NSA are largely indeterminate. Reynolds is also developing ass address this problem.

Proliferation

The second major problem with growing neural stem cells as neurospheres is that only about 10 per cent of tl turn into neurons. When the cells are given growth factors in culture to drive proliferation, it seems to push the predominantly down the astrocyte lineage (approximately 90 per cent).

Since generally only one to 10 per cent of transplanted cells survive, the numbers of cells needed for the trea one patient becomes unreasonably large.

"People have tried very hard and for a long time and push cells down the neural pathway and basically, it just work," he says.

Hence, a need existed for a more accurate way of determining and purifying precursors cells. "We have to kn what we are transplanting into patients."

Reynolds' team has come up with a new assay, called the neuroblast assay, which increases the number of r that are produced from neurospheres. These are then sorted to give a purity of about 90% neurons. The succ implementation of this technology also depends on being able to identify distinct population of cells within the heterogeneous population of stem and progenitor cells.

"We need to know exactly what is in the culture dish, and what each patient receives in a reproducible way."

Variable and indeterminate combinations of neuronal and other CNS cells are the most likely cause for the ne effects seen with those early transplants into Parkinson's patients. Part of the technology developed by the te QBI is focused on sorting the expanded cells to address this exact issue.

Ideally, they will be able to take stem cells from an adult donor, grow them up in tissue culture as neurospher out the neuronal and non-neuronal cell types, and then reproducibly transplant for each individual. The proce additionally allow controlled mixing of the sorted cells.

"You may not want to transplant all neurons - you may want to use 60 per cent neurons and 40% astrocytes. some transplant papers that report better results when neurons are transplanted with astroctyes."

The ultimate aim for this research is to have a renewable and defined source of neural stem cells that can be for different patients to treat spinal cord injury, stroke, Parkinson's disease and more.

"Obviously this is just the first step, but we now have a way of figuring out what we need to."

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Use of gene therapy in central nervous system repair.

Review article

Acta Neurologica Scandinavica. 109(1):1-8, January 2004.
Tinsley, R.; Eriksson, P.

Abstract:
Recent advances have increased our molecular understanding of the cer disease. In order to realize the clinical benefits of these findings, new mol such as CNS gene therapy. Although the field has suffered setbacks, it re new therapies in the post-genomic world. The development of new vecto models of CNS disease, provides evidence suggesting that gene therapy option. In fact, the first gene therapy clinical trial for Parkinson's disease h gene therapy has been applied in animal models, and how it may be use diseases and trauma in human beings. Furthermore, it explores how suc augment, more conventional therapeutic approaches.

Perspective

Nature Reviews Neuroscience 7, 75-84 (January 2006) | doi:10.1038/nrn1829

Opinion: Gene therapy: can neural stem cells deliver?

Franz-Josef Müller[1,2], Evan Y. Snyder[1] and Jeanne F. Loring[1] **About the authors**

Abstract

Neural stem cells are a self-renewing population that generates the neurons and glia of the deve proliferated, genetically manipulated and differentiated in vitro and reintroduced into a develo CNS. Neural stem cells have been considered for use in cell replacement therapies in various ne unexpected and potentially valuable characteristic of these cells has recently been revealed — th be attracted to areas of brain pathology such as ischaemic and neoplastic lesions. Here, we spec stem cells might be exploited as delivery vehicles for gene therapy in the CNS.

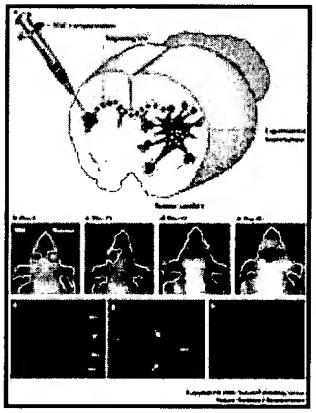
Neural stem cells can be defined operationally as cells that can continuously self-renew and hav

intermediate and mature cells of both glial and neuronal lineages[1]. There are various subpopula be restricted to particular developmental stages or regions of the mature brain, and each of thes specific biological features[2,3]. It remains unclear whether cultured cells that are derived from t operational definition of neural stem cells — multipotency and the ability to self-renew — are id have been reported in vivo. In addition, as there are few consensus criteria that can be used to d cells known as neural stem cells in one laboratory may differ considerably from similarly namec For the purposes of this review, we use an inclusive view, assuming that cells that are called neu investigators do have common features that allow generalization. However, we do add the cave: particular neural stem cell line or preparation might not apply to all populations (for more deta **3–6**; for reviews, see Refs **2**,**7**,**8**).

Neural stem cell homing and drug delivery

The migratory abilities of endogenous and exogenous neural stem cells are well known, and it h that these properties, along with the cells' differentiative abilities, might be harnessed for repla disease. In 2000, some reports showed for the first time how these cells might be used in a nov to deliver therapeutic substances to specific sites in the brain[9,10,11]. These reports showed tha transplanted into animal models of brain neoplasia were found near metastatic tumour cells far transplantation[9,10,11] (**Figs 1**,**2**). These observations suggest that neural stem cells engineere might be used to track down and destroy malignant cells. This opens up a possible new realm fo being viewed solely as restorative cell therapeutics, the cells could help to solve one of the most therapy — how to target therapeutic genes to diseased tissues.

Figure 1 | Neural stem cell homing in brain tumours.



a | Transplanted neural stem cells (NSCs) showing tropism for malignant cells in rodent models Exogenous neural stem cells implanted at sites distant from experimental brain tumours have b believed that this phenomenon could be exploited to track down widespread metastatic CNS pa therapeutic systems into brain malignancies. Panels show a time series for murine neural-stem- transfected with the 'luciferase' gene (Luc) and implanted into one hemisphere of experimental emission imaging of Luc expression for these animals is shown on day 9, day 15, day 22 and day experimental tumour (black circle in b) was evident from day 15. f–h | Pathotropism of human n cell line)[2]. f | Distribution of the cells (red) within a U87 (a glioblastoma cell line) xenograft (ar nuclei shown in purple). g | Distant tumour satellite of a U251 (a glioblastoma cell line) xenogra blood vessel is marked by an asterisk). Note that neural stem cells can migrate transcallosally fr also infiltrate small tumour satellites that have dislodged from the main tumour mass. h | Proxi

blood vessel (green) in a U87 xenograft. Panels b–e reprinted, with permission, from Ref. **82** © Panels f–h reprinted, with permission, from Ref. **23** © (2005) Neoplasia.

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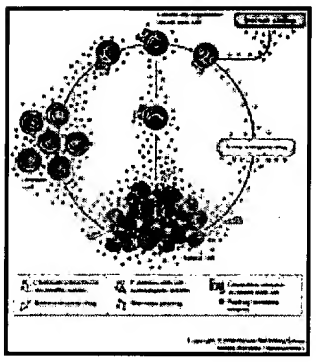
Figure 2 | Determinants of neural stem cell homing to brain tumours for delivery



Neural stem cells express various receptors for chemoattractant signals as a result of brain path chemoattractants are chemokines such as stromal cell-derived factor 1 (SDF1, also known as ch CXCL12) and monocyte chemoattractant protein 1 (MCP1, also known as chemokine (C–C moti chemotactic proteins such as vascular endothelial growth factor (VEGF). Stem cells can be gene enzymes that metabolize non-toxic prodrugs locally, thereby allowing production of the active f cytokines that act directly on the tumour or activate immune cells, which, in turn, attack the tur

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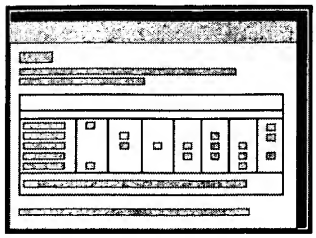
The characteristics of neural stem cells make them suitable as therapeutic delivery vehicles for (from other cell types that might be considered for this purpose. Unlike fibroblast cells, which m organs, neural stem cells have the potential to integrate seamlessly into the host brain without c example, neural stem cells could differentiate into glia or neurons, but are unlikely to become c stem cells can be propagated for long periods, and are therefore amenable to the techniques req Because stem cells can disperse throughout the brain after transplantation, the use of these cell preferable to multiple stereotactic injections for the delivery of molecules that require distributi enzyme replacement in lysosomal storage diseases[12]. Another characteristic of neural stem cell for targeted delivery is their tropic behaviour toward neoplasms, which could be exploited to ta infiltrating malignant satellites after main tumour resection.

Neural stem cell pathotropism

Neural stem cells (endogenous and transplanted) seem to be attracted to various experimental l such as cancers and areas of neurodegeneration. For example, neural stem cells have shown tro degenerating spinal cord motor neurons in a transgenic mouse model of **amyotrophic latera**

1). Neural stem cell cancer tropism is not limited to primary brain malignancies and has also be

Table 1 | Disease models with neural stem cell tropism



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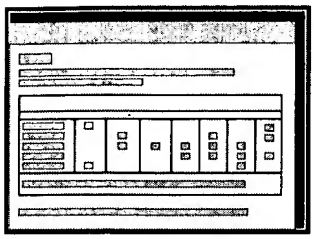
The fate of neural stem cells in the presence of lesions is not well understood, because most pre markers (for example, reduction in tumour burden or survival time after treatment)[9, 16]. In cer lesions, transplanted cells appear to form astrocytes and neurons[17]. A glial fate may not be idea neuronal differentiation that could participate in abnormal, possibly damaging, circuits.

The normal course of neural stem cell development and migration in vivo is controlled primaril regions of the brain that harbour neural stem cells. The microenvironments surrounding neural astroglia, microglia and endothelial cells, which are important regulators of stem cell generatio during maintenance of brain homeostasis[18, 19, 20, 21, 22]. Disturbances in the environment due affect stem cell behaviour by disrupting the environmental equilibrium and exposing the cells t encounter. For example, gradients of factors such as vascular endothelial growth factor (**VEGF**) (**SDF1**), which emanate from distant brain lesions, may act as attractants for stem cells[23, 24].

In attempting to predict the behaviour of stem cells in the brain, it is important to consider both that are transplanted to the brain. Endogenous and transplanted neural stem cells are often fou pathology, but there are some important differences to keep in mind. Cultured neural stem cells expanded in culture well beyond their expected proliferative capacity in vivo. Because culture c the phenotype of cells, culture could markedly alter the cells' response to their environment wh of a recent study showed that exposure to the mitogen epidermal growth factor (**EGF**) may con phenotype to neuronal progenitors[4]. Until more is known about the receptors expressed by neu effects on genetic, epigenetic, transcriptional and translational levels, information about exoge cautiously to interpretations of endogenous stem cell behaviour[5, 6, 8].

The molecular basis of neural cell pathotropism is not well understood and different pathologie Cultured neural stem cells express a wide variety of receptors that should enable them to respo emanate from brain pathologies (**Table 2**). Experimental studies show that they home to locali transplantation (**Table 1**). Some factors that can be held responsible for this phenomenon belo [25, 26] (chemotactic cytokines; **Table 2**). Chemokine and cytokine production is a common feat stroke and brain malignancy, which suggests that these factors could be important in mediating pathology[24, 25, 26].

Table 2 | Cytokines potentially involved in neural stem cell pathotropism



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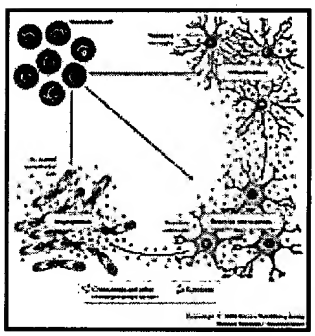
Regulation of neural stem cell tropism

The available information suggests that there are at least three important physiological processe behaviour of transplanted neural stem cells: inflammation, reactive astrocytosis and angiogenes

Figure 3 | Determinants of neural stem cell pathotropism.



Neural stem cells are attracted by at least three physiological processes that are common to mar reactive astrocytosis and angiogenesis. Pathology-induced CNS inflammation is mediated by act cytokines and chemokines, which, in turn, increase the inflammatory reaction (for instance, the interleukin-6, **IL-6**, and monocyte chemoattractant protein 1, MCP1, also known as chemokine gradients can also attract neural stem cells. The brain lesion and subsequent inflammation trigg to signals emanating from inflammation, activated astrocytes secrete chemotactic factors (for ex SDF1, also known as chemokine (C–X–C motif) ligand 12, CXCL12, and vascular endothelial gr can act both as chemoattractants for neural stem cells and as promoters of pathology-induced a angiogenesis and inflammation-activated endothelial cells enhance neural stem cell homing to l chemoattractant factors (such as SDF1), and also offer an atypical, perivascular niche for suppo

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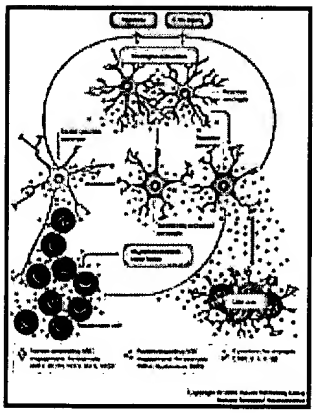
Inflammation. In vitro, microglia can induce neural stem cell migration[22, 27]. It is an attract

inflammatory response to brain pathology is the common denominator responsible for the seen cells to disparate brain lesions. The prevailing view, based on studies of multiple sclerosis, epile encephalitis and brain irradiation, is that brain inflammation is detrimental to the CNS in gene[29,30,31]. Microglia are the first line in defence against brain pathologies, functioning as a dam and responding to insults by producing cytokines, which, in turn, initiate further reactive respo cells also release neurotrophins[29,33], which would be expected to protect neurons, and microg can modulate the mobilization of neural stem cells both in vitro and in vivo. This suggests that r initiating and coordinating neural-stem-cell-based brain repair mechanisms[22,27,29,34].

Reactive astrocytosis. As inflammatory cytokines are released by microglia in response to a astrocytosis, characterized by hyperplasia, hypertrophy and an increase in glial fibrillary acidic [36]. Triggers and mechanisms of this multifaceted response are not fully understood, but some f proximity of the astrocytes to a CNS pathology, the type of lesion and the types of cytokine prod (IL-1β))[35,37].

Studies of the acute effects of inflammatory signals suggest that certain types of activated astroc tissue regeneration and stem cell migration[38,39,40] (Fig. 4). For example, reactive astrocytes SDF1, which is at least partially responsible for the attraction of neural stem cells to these lesion involved in the guidance of leukocyte and glial homing toward brain injuries[41,42] and can reve invoked by tissue damage to a phenotype resembling radial glia in the developing brain[43]. Thes progenitor migration[43]. Although some types of glial activation might have beneficial effects, it reactive astrocytes are thought to interfere with neuronal–glial signalling and impede neural pr scars and secreting factors such as slit homologue 2 (SLIT2), tumour necrosis factor-α (TNFα) hyaluronic acid[44,45,46].

Figure 4 | Model of activated astrocyte mediation of neural stem cell homing to br



CNS injury, hypoxia, microglial activation and the subsequent release of inflammatory cytokine 6 and ciliary neurotrophic factor (CNTF)) invoke complex responses known collectively as glios injury, some mature glia revert to a developmental, radial-glia-like state, and can directly media towards brain lesions. Cytokine release also causes transient activation of astrocytes. These tran source of chemoattractants (such as stromal cell-derived factor 1 (SDF1), vascular endothelial g chemoattractant protein 1 (MCP1)) that act on neural stem cells (NSCs)[3,4,5,6]. SDF1 may dire

toward brain pathology along non-stereotypical routes[4]. Other factors (such as fibroblast growt growth factor 1 (IGF1)) supplied by reactive astrocytes support neural stem cell proliferation, su astrocytes proliferate reactively, become hypertrophic and increase their glial fibrillary acidic pr eventually results in the formation of a tightly compacted astrogliotic scar, which is the source o (SLIT2), tumour necrosis factor-α (TNFα) and hyaluronan) that repel neural stem cells and migl regenerative capacity[3, 8, 9].

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Angiogenesis. Evidence is emerging for an intimate relationship between CNS morphogenesi basal lamina produced by endothelial cells contains many components that are believed to be in neurogenic niche[21, 49]. Therefore, endothelial cells could also be involved in the regulation of tl pathology. Vasculogenesis resulting from brain pathology could enhance neural stem cell mobil chemoattractants such as VEGF. VEGF-mediated homing of stem cells might have a key role in stem cell glioma tropism[23, 50, 51]. In addition, SDF1 is expressed by endothelial cells as well as could be important for attraction of neural stem cells[24]. Because neural stem cells seem to inter endothelial cells from the luminal side, adhering and transmigrating in a similar fashion to leuk can be delivered via the bloodstream. In support of this idea, a recent report shows that neural s bloodstream in a mouse model of multiple sclerosis establish atypical niches around blood vess undifferentiated state and appear to suppress the inflammatory process[53, 54].

Choosing a vehicle for delivery

There is considerable diversity among neural stem cell lines and they may not all be equally suit stem cell delivery vehicle would be stable in tissue culture and capable of sustained, preferably r molecules. The cells should have predictable and appropriate differentiation patterns in culture survive long term in vivo without forming tumours. For the therapeutic strategy to be effective, demonstrate responsiveness to the chemotactic signals produced by the type of pathology that t would be a means for facile delivery of the cells (for example, via the bloodstream).

Should cell lines be immortalized? Historically, non-tumour cells had to be immortalized sufficiently to facilitate their characterization. Immortalizing cells usually involves introduction to expand beyond the time at which they would normally reach senescence. Identification of gro culture of non-immortalized neural stem cells has made immortalization less necessary, and the immortalized cells as research tools and in clinical settings. Immortalized neural stem cells app atypical of most neural stem cell populations, such as extraordinary migratory abilities in vivo (and a higher degree of multipotency, which may increase the probability of tumour formation b

However, there are some cases in which oncogene immortalization is an asset. Safety concerns r value of the more pronounced invasiveness and migratory capabilities of immortalized neural st immortalization can allow propagation of cells with definable properties almost indefinitely, so particular traits can be established. Furthermore, if immortalized cells could be shown to be reli much easier to control their quality than the quality of primary cell preparations for use in clini could be subjected to much more thorough analysis.

Primary cells for transplantation. Although it can be argued that the ideal cell type for tr the endogenous neural stem cell as possible, there are some serious limitations to the use of pri stem cell reconstitution of bone marrow, it is unlikely that a single neural stem cell or small gro regenerate damaged brain tissue, so expansion of cells in culture will be required. How much ex sufficient number of viable stem cells for a successful transplant has to be determined empirical

In vitro culture creates its own problems. There are many neural stem cell lines and preparatio under different conditions from diverse sources and maintained under a wide variety of culture to be used clinically, an important challenge will be for investigators to agree on a common set c characterization criteria.

Human embryonic stem cell-derived cells: can they be effective and safe? Human e several powerful advantages over other types of stem cell for therapeutic approaches. ES cells a cells of the inner cell mass of blastocyst-stage embryos. Unlike neural stem cells, differentiation elements of the nervous system. ES cells are also immortal and do not undergo senescence after Perhaps most importantly, the focused efforts to characterize ES cells in many laboratories mea the same well-studied cell populations. This reduces the problems of reproducibility and quality with other stem cells. Human ES cells can be induced to differentiate along neuronal lineages[59] they resemble somatic neural stem cells. However, there are several important challenges that a therapeutic approaches. First, we have to anticipate that because they have not experienced nor cells might not develop conventional cellular phenotypes, and this may result in unpredictable c much data are available on the migratory potential of human ES-cell-derived neural stem cell p neural stem cells. Furthermore, populations of ES-derived transplanted cells must be shown to characterize undifferentiated populations. It is also important to keep in mind that the use of E concerns associated with the derivation of these cells from early embryos.

How will we decide? The decision for or against a certain cell preparation must be based on harm, and the modern concept of evidence-based medicine. At present, a widely held view is th be the most relevant therapeutic systems for targeting brain pathologies. However, there is insu any cell type, and there is a need for comprehensive studies that compare different cell populati New approaches, such as improved in vivo cell tracking tools, will be important for resolution o

Neural stem cell-based gene therapy

In the nervous system, replacement of neurons is often considered to be the main goal of cell th cells, are already being used as gene delivery tools and for rescuing neurons rather than replaci gene therapy is that diseases that are caused by the lack of some crucial protein can be treated b appropriate gene expression vectors. This idea was originally proposed for hereditary diseases s In these diseases, a mutated catabolic enzyme causes a metabolic logjam in the upstream pathw affected cells and surrounding tissue with accumulating substrates and toxic side products. In t expression of a functional replacement gene in or near the affected area would restore the meta defined concept has been broadened to include any genetic manipulation of cells or tissue to tre gene therapies for **Alzheimer's disease** include targeted expression of choline acetyltransfera acetylcholine, which therefore results in the localized delivery of small molecules, in this case ac cells will be used therapeutically depends on the nature of the disease or damage that requires t

Neural stem cells can be genetically transduced in vitro and in vivo[12, 64]. Currently, the most ef introducing genes into neural stem cells is by means of lentiviral vectors; the chief concerns abo

transgene silencing in situ and that integration of the transgene can activate a nearby oncogene, growing subclones[58, 65, 66].

To highlight various stem cell-mediated gene delivery strategies, we discuss in more detail six e: system that may benefit from such therapy.

Parkinson's disease. A lack of dopamine in the putamen (caused by the degeneration of inn nigra) has a central role in the pathogenesis of **Parkinson's disease** (PD). Systemic L-DOPA (an effective treatment for the symptoms of PD early in the course of the disease, but does not pr degeneration and eventually becomes ineffective. Because the degeneration is relatively localize cell therapy, and experimental transplants of fetal dopamine neurons into the putamen were pi patients, the successful transplants seemed to work as dopamine pumps, similar to the systemic the chief advantage of a transplant being a smoothing of the on–off cycle of symptoms, in which being unable to move and periods of uncontrollable movement[67, 68]. A concern about this appr variability, which is partly due to the inconsistency of the fetal tissue used for transplant and is characteristics of the disease in each patient; in a controlled study, the best therapeutic benefit best achievable symptomatic improvement using L-DOPA in the same patient[68]. The mechanis not clear; because of the paucity of functional connections in many transplants, it has been pro were acting more as gene therapy vehicles for dopamine delivery than as replacement neurons. might not be limited to acting as dopamine pumps; in some cases, functional connections have suggested that the transplanted cells may produce trophic factors that help to protect remainin preclinical investigations are testing the use of genetically induced production of neurotrophic f neurotrophic factor (**GDNF**) or VEGF in neural stem cell transplants[69, 70, 71] (see also the foll neurotrophic factor delivery in neurodegenerative diseases).

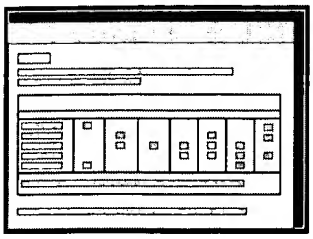
Alzheimer's disease. Alzheimer's disease presents a greater therapeutic challenge than PD, b is widespread, beginning in the hippocampus, cortex and amygdala, and progressing to other re strategies for cell and gene therapy are focused on using cells to deliver neurotrophic factors. N protect neurons from degeneration and to re-activate impaired circuitry in neurodegenerative d trial using fibroblasts to deliver nerve growth factor (**NGF**) has recently been completed[72]. An associated virus (AAV) to deliver NGF expression vectors directly to the brain.

Most recently, we have proposed that the homing qualities of neural stem cells might be exploit with therapeutic enzymes (F.-J.M. and J.F.L., unpublished observations).

Amyotrophic lateral sclerosis. Experimental studies show that overexpression of growth f growth factor 1 (**IGF1**) or VEGF can have beneficial effects on the course of ALS in animal mod this sort of therapy for clinical use is the delivery of these large molecules across the blood–brai to be the best means of increasing the production of these factors in situ. Cell therapy might be these large proteins to specific areas of the CNS where they can aid in the survival of neurons[75].

Brain malignancy. Neural stem cells seem to be attracted to certain brain tumours and this allowing these cells to be used for local chemotherapy (**Fig. 2**). The main issues under investiga optimal choice of stem cell type, and the most effective therapeutic system to use (**Table 3**). So immortalized neural stem cell-like cells in preclinical models. The large variety of therapeutic s viruses, prodrug-converting enzymes, immunomodulatory cytokines, proteins with anti-angiog direct anti-tumoural activity[9, 10, 11, 76, 77].

Table 3 | Examples of studies on neural stem cell-based gene therapy in animal mo



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Disorders of brain metabolism. Inborn genetic defects affecting the CNS, such as lysosom most promising targets for stem cell therapy. Dispersion of genetically normal stem cells in the delivery of missing enzymatic activities[12, 78]. The current preclinical research objectives for this timing of treatment, which could be in utero, and the type of stem cell to use. The most straightf storage diseases that are frequently accompanied by an extremely prominent neuroinflammato galactocerebrosidase deficiency (**Krabbe disease** in humans and the twitcher mouse). Signific recently in protecting neural stem cells from inflammatory damage and could be applied to this

Neuropathic pain. The delivery of cells and genes to treat certain forms of neuropathic pain i **3**). Potentially therapeutic molecules such as growth factors and neurotransmitters delivered by alleviate forms of chronic pain in animal models. An emerging conceptual aspect of these studie derivatives — astrocytes and oligodendrocytes) might have another unexpected application; the injury-induced central pain by influencing neuronal circuitry and excitability[80, 81].

From the pioneering work in PD to the emerging exploration of stem cell therapy for Alzheimer enthusiasm for the potential of stem cells for the treatment of various diseases of the nervous sy delivery has the potential to maximize the therapeutic impact of drugs. However, most stem cell still in the preclinical testing phase and will have to pass significant hurdles to become viable th

Summary

Neural stem cells could be exploited as delivery vehicles for therapeutic molecules to treat CNS towards brain pathology, which appears to be mediated at least in part by chemokines. The chal of this approach are in determining which neural stem cells are appropriate for each application delivered, and what diseases are suitable targets for this approach.

It is important to remember that the current dominant concept in this field predicts that neural for cell replacement therapy. Although experiments continue to be designed with the expectatio yield surprising new interpretations. We will benefit from remaining receptive to unconventiona that will lead us to future discoveries that we cannot imagine today.

Links

DATABASES

OMIM

- **Alzheimer's disease**
- **Amyotrophic lateral sclerosis**
- **Krabbe disease**
- **Parkinson's disease**

Entrez-Gene

- **VEGF**
- **SDF1**
- **EGF**
- **GFAP**
- **IL-1β**
- **SLIT2**
- **TNFα**
- **GDNF**
- **NGF**
- **IGF1**

FURTHER INFORMATION

- **Clinical trial results, Alzheimer's Disease Education & Referral Center**
- **The official National Institutes of Health resource for stem cell research**

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Review

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International spinal research trust research strategy. III: A discussion

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Abstract

Study design:

Discussion document.

Objectives/methods:

To review the Research Strategy of the International Spinal Research Trust (ISRT), which ident research that are likely to be beneficial in developing potential treatments for spinal cord injury intended to both guide the programme of research towards areas of priority and stimulate discu research. This latest document has been developed to take into account the scientific progress i previous Research Strategy.

Results/discussion:

The latest scientific developments in research designed to repair the spinal cord and restore fun might impact on spinal cord injury research are highlighted.

Sponsored by:

ISRT.

Keywords:

spinal cord injury, regeneration, ISRT

Introduction

The International Spinal Research Trust (ISRT) is committed to developing treatments to cure t injury. For over 25 years it has pursued this goal by funding scientific research proposals from b recently, it has recognised the need to improve the scientific basis for assessment of spinal cord committed funding to developing such techniques and training scientists in their use. It is inten measures will provide a resource for use in clinical trials worldwide, and will enhance the detect recovery in such trials.

The record of achievement of the ISRT in promoting basic and clinical research leading to poter injury is second to none: it is the pre-eminent UK organisation in this area, and funds internatic

Although by no means the largest funding organisation in this area, ISRT is consistently at the f and has developed an enviable reputation for 'punching above its weight' compared with larger the reasons for this is the ISRT Research Strategy, which has been developed by the Scientific C efforts in particular areas of research.

The first ISRT research strategy document was published in by Harper *et al* in 1996,[1] and was r the second research strategy.[2] These documents established a coherent research strategy by ana attention in order to achieve the overall objectives of the ISRT – to repair the damaged spinal cc strategy documents identify key areas for funding and support, which enables basic and clinical proposals, and the Scientific Committee and external reviewers to judge each proposal accordin programme of research to be steered towards areas of priority. In addition, the document has pı

The unprecedented success of spinal cord injury research in the past few years has resulted in si were not covered by the previous research strategy. Consequently, ISRT have updated this docu progress.

The following document, which identifies priorities for basic and clinical research in the coming read in conjunction with, the existing research strategy.[2] In general, ISRT expects applications i influenced by and to refer directly to the themes described in this strategy document, but also re novel approaches as they are developed.

In addition to promoting experimental and clinical studies, ISRT considers it vital to promote ir scientists and clinicians on the merits, risks and scope for interventions in the aftermath of SCI inflammatory, anti-proliferative, neuroprotective and immunosuppressive drugs. This should ir testing capabilities of existing large study groups worldwide, for example, via the International (Paralysis (ICCP) Clinical Trials Workshops (**http://www.campaignforcure.org**), the Europ (**http://emsci.org**) and the North American Clinical Trials Networks (**http://www.christopherreeve.org/site/c.geIMLPOpGjF/b.1048737/k.322D/North** with a view to fostering well-founded clinical best practice.

The targets that form the Third ISRT Research Strategy Document reflect current progress in sp

were highlighted in the earlier Research Strategy, whereas the importance of others has been re previously, overall strategy is divided into two themes: the vertical targets represent experimen capabilities indicate the means by which the vertical targets are likely to be fulfilled.

Vertical targets

- VT1. Early trauma/inflammation and scar tissue
- VT2. Inhibitory and facilitatory influences
- VT3. Guiding regrowth
- VT4. Spared spinal cord cells and fibres
- VT5. Cell- and gene-based therapies
- VT6. Combinatorial therapies
- VT7. Complementary therapies

Horizontal capabilities

- HC1. Animal models
- HC2. Measuring regrowth and restoration of connectivity
- HC3. Clinical trials
- HC4. Collaborative research

Vertical target 1

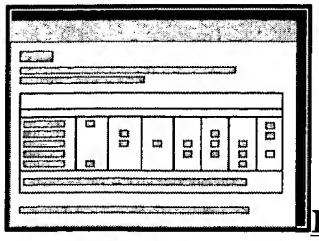
Minimising the deleterious effects of early trauma, inflammation and scar tissue

Much of the post-traumatic tissue damage and subsequent neurological deficits associated with events that are initiated by the original injury. Thus, spinal injuries comprise a primary zone of secondary injury, and neuroprotective strategies that either reduce or prevent the spread of sec greater recovery of function.[3, 4, 5] Many of the mechanisms responsible for these secondary pro further understanding of the detailed molecular and cellular mechanisms involved in early trau glial scarring is vital to provide direction for the rational development of therapeutics to minimi function following injury. This is the rationale behind treatments such as methylprednisolone,[6] as GM-1 gangliosides (which also promote plasticity)[7] and newer developments such as the tetr

Spinal cord injury should not be regarded in isolation. There are similarities in the mechanisms ischaemic and traumatic brain injuries,[9] and some potential therapeutics have already been tes brain injury. The lessons learned from these (relatively unsuccessful) trials should provide valu injury community regarding clinical trial issues such as the need for controls and careful dose st Therefore, in addition to developing new therapies, an important role of the ISRT is to promote and clinicians, and the critical evaluation of the merits of these existing and potential treatment

However, because most neuroprotective strategies have not had particularly substantial effects i priority to increase the understanding of cell death after acute spinal injury and the conditions t (**Table 1**; VT1.1), in order to develop newer, more powerful therapies.

Table 1 - Vertical target 1: Minimising the deleterious effects of early trauma, infla

 **Full table**

It remains important to characterise the effects of injury on major spinal cord components, sucl white matter, the composition and effects of the glial scar, vascular effects and the role of inflam mechanisms of secondary cell death, and the factors that lead to cyst formation (**Table 1**; VT1.1 the contribution of these events to functional deficits (**Table 1**; VT1.2), and to accurately and m therapeutic agents on spinal cord function and behaviour. It should then be possible to develop both by rational mechanistic drug design and by screening drug libraries in appropriate models models, it is also necessary to further our understanding of human spinal injury (**Table 1**; VT1.; markers of early traumatic injury in humans (**Table 1**; VT1.4).

Exclusions and future issues

Work in non-spinal cord models should be explicitly justified. Funding for the acquisition of ne inflammation etc. outside the spinal cord, for use in SCI research, will be considered under this Horizontal capability 4.

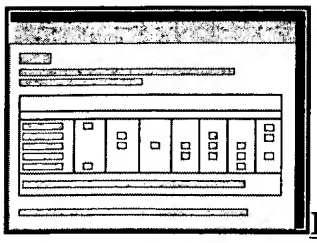
Vertical target 2

Inhibitory and facilitatory molecules

The inhibitory effects of the CNS on axon growth are well documented, as is the ability of peripl regeneration. The consensus is that there are several possible reasons why peripheral nerve gra first is that inhibitory cues that are present in the CNS are absent from the PNS. The second is t neurotrophic factors and contain other regeneration-promoting proteins such as cell-surface pr inhibition. A third possibility is that inhibitors that are present in PNS grafts are localised and r regeneration. Thus, it is established that chondroitin sulphate proteoglycans (CSPGs), some my present in both the PNS and the CNS, but their expression, stability and localisation/cellular dis some types of CNS neurons do not grow into peripheral transplants.[11] This may be because of tl grafts, or because these CNS neurons are unable to mount an appropriate response of regenerat

Therefore, research into inhibitory and facilitatory molecules falls into three categories: the disc to inhibition and facilitation of axon growth (**Table 2**; VT2.1), the production of reagents that e increase facilitation (**Table 2**; VT2.2), and the investigation of how other approaches, such as c interact with inhibitory/facilitatory molecular mechanisms (**Table 2**; VT2.3).

Table 2 - Vertical Target 2: Research into inhibitory and facilitatory molecules.

 **Full table**

The idea that the presence of inhibitory molecules causes regeneration failure was proposed by culture[12] and then in the injured spinal cord,[13] on the basis of a molecule present on the surfac molecule is now known as Nogo. Blocking Nogo promotes either regeneration[13] or beneficial sp

Nogo is one of several inhibitory molecules that are associated with CNS myelin, with other can glycoprotein and oligodendrocyte myelin glycoprotein. Subsequently, inhibitory molecules of th families have been found to be associated with astrocytes and fibroblasts[16, 17, 18, 19, 20] and a c these various inhibitory molecules has been described.[21] It is likely that increased molecular ch inhibitory pathway will help in the development of new therapies.

In addition to the lack of inhibitory molecules, it is proposed that peripheral nerve grafts suppo secretion of trophic factors. Many studies have shown that growth factors upregulate RAGs and growth,[22, 23, 24] and genetically modifying transplants to overexpress neurotrophic factors mig Thus, an effective combination that enhances positive factors and reduces negative ones is an at

So far the molecular response to neural injury has been studied mainly at the level of changes in proteins. This has led to the discovery of several molecules that are important in regeneration. T projects have identified most human and rodent genes. This enables high-throughput screening proteins, which will be instrumental for elucidating the molecular mechanisms that underlie re in a more complete picture of the molecular changes that occur in neurons and glial cells after i of proteomic techniques coupled to web-based databases and data-analysis tools is likely to ide to pinpoint novel targets for pharmacological and cell- and gene-based intervention strategies. processes that underlie regeneration is still very limited, so incorporating genomic and proteom neuroregeneration research is vital to progress in this field.

Vertical target 3

Guiding regrowth and establishing appropriate connections

Several existing therapies promote the regeneration of injured axons in long, white-matter path being developed to bridge spinal injury sites using synthetic biomaterial implants.[26, 27] Howev special environment that these therapies provide, to cross scar tissue associated with the injury beyond the scar has proved a major problem.

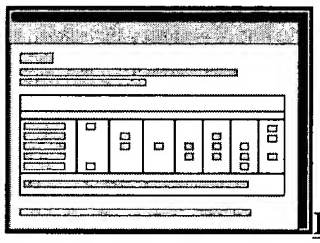
Given that the number of axons that do regenerate and regrow is likely to be small compared wi important to understand how fibres behave once they have reconnected with the spinal cord be extreme, it might not be necessary to guide regrowing fibres to their appropriate targets if intrin CNS can exploit any connectivity to achieve some recovery of function. At the other extreme, ne ineffective or even add to secondary problems such as spasticity and increased pain levels. We a factors that guide axons to their eventual target by attraction and repulsion, including factors th

tracts until they descend (or ascend) to the level appropriate to penetrate the grey matter.[28, 29] matter, ephrins, netrins, semaphorins and related molecules guide axons and regulate midline c termination.

It is probable that the main national research funding bodies will continue to invest in this area expanding the 'library' of agents that guide growing and regrowing axons. ISRT should adopt a knowledge into spinal injury studies and promote research into:

- The nature and temporal course of new synaptic connectivity after SCI, using histological (**Table 3** ; VT3.2).
- The key guidance/trophic factors – how they are affected by SCI, particularly in regions al (**Table 3**; VT3.1, VT3.2), and whether their expression can be modified to encourage appr VT3.3).
- The potential of axonal sprouting and synaptic plasticity for regeneration and useful re-in
- The ability of trophic factors to restore axonal growth *per se* and to influence the re-establ (**Table 3**; VT3.4).

Table 3 - Vertical Target 3: Guiding regrowth and establishing appropriate connec



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Vertical target 4

Assessing the natural history of SCI and optimising spared spinal cord cells and ne

Except for a few open or penetrating injuries, there is spared spinal cord tissue in most cases of complete. Tissue sparing has important consequences, both in terms of the function of the resid plasticity. In animal models, fibres passing through the ventrolateral funiculi, including reticulc important for functional recovery of hindlimb locomotor function.[31] In humans, the importanc clear, while damage to corticospinal fibres has more serious effects.[32]

The minimal sparing of white matter, in terms of either area or axonal number, that is compatil cats,[33] <25% for non-human primates[34] and <10% for humans.[35] Minimal deliberate moveme dorsal and plantar flexion of the foot, has been reported in humans with only 3.5–10% of cortic level.[35] The idea that a limited number of nerve fibres is sufficient for function has encouraged formulated in the belief that a few new axons that cross the lesion site and connect somewhere recovery.

After total spinal cord transection in laboratory animals, weight-supported, unassisted stepping circuitry below the level of the transection, without supraspinal control.[11] This is not the case in motorneurons pools can be activated by proprioceptive sensory inputs generated by treadmill e cases of incomplete SCI.[36] The surviving supraspinal motor input to the spinal cord is insufficie

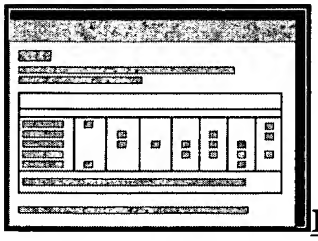
muscles of a single joint or to simultaneously inhibit antagonist muscles, which indicates that v partially related to function.[37] After complete SCI, it appears that local, segmental, propriocept generate patterned muscle activity, but not in a sustained manner.[36, 38]

In animals and humans, plasticity in the motor systems has been shown at different levels from Erroneous connections made after an injury persist for many years.[40, 41] Early after the injury that might be occupied by either inappropriate supraspinal tract axons or local interneurons. Th the development and establishment of aberrant reflexes that might be counterproductive in eith function, for example, spasticity or aberrant reflexes. In addition, the occupation of these sites b might prevent appropriate regenerating fibre systems reconnecting to the right circuits. One wa specific neuromodulatory treatments. The development of techniques that maintain the neuron as far as possible within its 'normal' state, and thereby prepare this tissue for successful interve

Plasticity in the sensory systems, such as collateral sprouting, is well known and might account of sensation below the level of the lesion and the development of neuropathic pain. Imaging stu sensation after SCI is accompanied by reorganisation of the somato-sensory cortex.[42, 43] Howe explain referred sensation from the viscera perceived in deafferentated areas. Nevertheless, larg other CNS sites such as thalamus, brain stem, cuneate nucleus and spinal cord.[44, 45, 46, 47] Thi pre-existing connections[48] and actual axonal sprouting.[49] To achieve functional recovery of se considered include manipulating the biological environment to promote regeneration and funct strategies that increase reorganisation in the CNS.

It is important to define the structure and function of the remaining spinal cord tissue (**Table 4** enhance its functional capacity most effectively (**Table 4**; VT4.2, VT4.3). The clinical consequ and below the lesion site compared with damage to long fibre systems remains to be establishe treatments that are designed to replace lost neurons are to be considered alongside those that l Even if nonfunctional, remaining tissue might have a valuable role in the effects of future interv as a scaffold for new growth.

Table 4 - Vertical target 4: Assessing the natural history of SCI and optimising spa fibres.



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Vertical target 5

Cell- and gene-based therapies

Since the last strategy review in 2000,[2] major progress has been made in the areas of cell and g includes grafting with fully differentiated tissue such as peripheral nerves, inflammatory syste macrophages, CNS-resident cells such as oligodendrocytes and olfactory ensheathing cells, and Stem cells are attractive theoretically because it is envisioned that they will respond to cues and

organ systems, such as the foetal liver following injury and adult heart tissue after cardiac infarc embryonic stem cells are less appropriate because they can develop into cancerous teratomas. T and tissue of both foetal and adult neural origin are preferred currently. Gene-based therapies h a therapeutic gene is expressed directly in the injured spinal cord or neural transplants are gene transplantation.

Cell-based therapies

Cell-based therapies might act in several, distinct ways: (i) as a potential source of either trophi improve the function of pre-existing spinal cord neurons; (ii) transplanted stem cells might dev remyelinate regenerating axons; (iii) transplanted stem cells might develop into functional spin those damaged by injury; and (iv) transplanted cells can serve as a substrate to support axonal g mechanisms predominate in studies that have reported restoration of spinal cord function and i types act in different ways. The use of cells as a source of multiple trophic factors to provide the for neuronal regeneration impacts on Vertical targets 2–4.

There has been some work to identify the cell types that are generated *in vivo* after stem cell tra undifferentiated, neurospheres in culture can generate all types of neural cell. However, althoug survive when grafted into the rat spinal cord, they only differentiate into astro- and oligodendro the adult spinal cord provides the molecular cues for glial, but not neuronal, differentiation.[50, 5] procedures for differentiating, isolating and transplanting them need to be perfected. Disappoir transplanting neural stem cells leads to an increase in pain levels (allodynia), which is associate the spinal cord. However, forcing stem cells into a distinct lineage before transplantation avoids outcome.[52] The benefits of grafting differentiated, purified cells require further study. These da that preclinical studies should specifically examine the adverse effects of cell therapies.

Cell-based therapies require that the cells are readily obtainable, easy to expand and bank, and s sufficient and appropriate axonal repair. Until large-scale, well-characterised adult and differen available, bone marrow mesenchymal stem cells (MSCs) are an attractive source that allows aut subject receives their own bone marrow. Transplanted unpurified MSCs improve remyelination after spinal cord injury, and several studies achieve modest functional recovery.[54, 55, 56] Differ as Schwann cells might further improve the outcome,[57] as might selection of MSCs from differe produce similarly effective cells, presumably because of the repertoire of cytokines and modulat

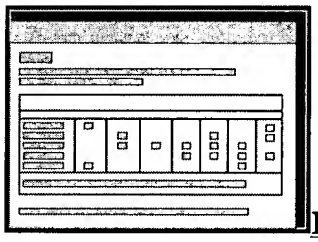
An alternative source of adult transplantable cells with repair potential are olfactory ensheathin generated from cultures of primary olfactory tissue: although both are essential for the reparati relationship of the two cell types is not fully understood.[60] Olfactory ensheathing cells encoura However, they are likely to be more effective when combined with other treatments (see vertical inhibitory cues of the scar tissue with chondroitinase ABC and providing a Schwann cell bridge ensheathing cells promotes greater functional recovery in a rat model than these treatments ind

Gene therapy

The first viral vectors used to express a therapeutic gene in the nervous system were imperfect t response. These problems inspired the development of improved 'minimal' vectors based on ad These viral vectors carry a transgene under a strong viral or cellular promotor, but are virtually Adeno-associated viral-vector-mediated expression of neurotrophins has been successful in res root avulsion and reversing atrophy of chronically lesioned rubrospinal neurons.[62, 63] In additi gene transfer, cellular transplants have been genetically modified *ex vivo* before transplantatior guides. The steady advances made in combining new viral vector systems with a range of promi holds fascinating perspectives for the development of new spinal cord repair strategies (reviewe

Although there has been much progress in the area of cell therapy, significant questions remain in gene therapy are: (i) how to enhance the level of expression of the transgene; (ii) control of th (iii) the difficulty in predicting and controlling the cell types that are transduced, and some cells then others (eg scar tissue can hardly be transduced for, as yet, unknown reasons); and (iv) the and dominant-negative proteins to overcome local action of inhibitory proteins is in its infancy. powerful technique that might be used to overcome inhibition and to enhance the expression of

Table 5 - Vertical target 5: Cell- and gene-based therapies.



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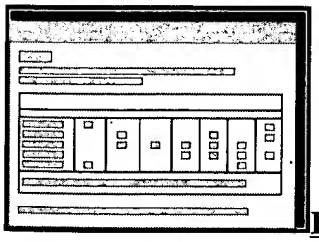
Vertical target 6

Combining therapies

Several independent mechanisms contribute to the outcome of SCI. Therefore, it seems reasona are directed at one specific injury mechanism are likely to have limited overall efficacy, and that might achieve a greater benefit and increase recovery.[61] Some published studies have combinec plasticity-promoting drugs to provide proof-of-principle of this concept. It is likely that more ef and combination therapy is likely to be a cornerstone of future strategies following SCI. Howeve between different interactions, interpreting the effect of combining potential treatments require

The potential complementarity of different therapies is crucial, and funding will only be conside cogent case for combining individual approaches (**Table 6**).

Table 6 - Vertical Target 6: Combining therapies.



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Vertical target 7

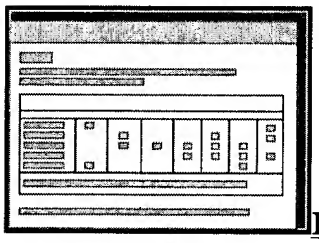
The complementary role of different forms of electrotherapy for recovery of funct

The aims of ISRT is to develop a long-term, effective treatment for SCI, based on better underst neurobiological mechanisms of injury and repair. Originally, therefore, functional electrical stin electrotherapy and intensive physiotherapy were not considered central to the research strategy involve actual repair of the injury. However, in the past few years ISRT and the SCI community position.

The primary purpose of FES is to activate paralysed groups of muscles; for example, FES impla control and to assist standing, locomotion and hand grasp. However, it is clear that, in addition also has long-term 'secondary' effects on central sensorimotor mechanisms[65, 66] that affect pla surviving fibres to make a greater contribution (see Vertical target 4).

A related point is that the development of the normal spinal cord and, probably, regeneration o least in part, activity-dependent processes; electrotherapy methods can be used to promote neu injury, which cannot be generated voluntarily by the patient. Finally, we know that activity in th above the level of the spinal injury, including the cerebral motor areas, cerebellum and basal ga SCI and show different patterns during both attempted and imagined movements. Thus, FES, r electrotherapy might all complement other, more invasive therapies and boost therapeutic effec (**Table 7**).

Table 7 - Vertical target 7: The complementary role of different forms of electrothe after SCI.



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Some forms of FES are invasive (eg sacral or lumbar root stimulators and intraspinal microstim refuse such implants because they expect a more permanent cure to be developed in the future chances of inclusion in future trials and treatment.

Given that the principal aim of ISRT is a long-term treatment that provides effective repair of S development of FES and other electrotherapeutic approaches? ISRT should promote research i

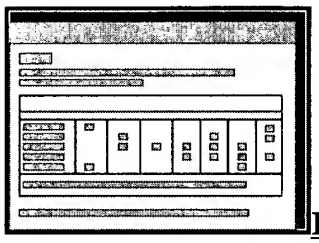
- Approaches that demonstrate the complementary role of FES in improving outcome of otl activity-dependent plasticity.
- Studies to determine the extent to which defined FES paradigms improve real-world tasks individuals with SCI.
- The use of noninvasive methods that offer clear prospects of functional recovery, especiall central activity-dependent plasticity.
- Improved outcome measures to assess functional improvements provoked by noninvasive
- The development of long-term, stable, electrotherapy techniques that complement other t

Horizontal capability 1

Animal models

Effective experimental models are crucial for understanding the basic biology of SCI and develo (Table 8). Two common approaches are to use (i) a model that aims to mimic as closely as poss clinically (ie contusion injuries), and (ii) a model in which specific tracts or pathways are lesion particular system to injury and its capacity for regeneration. Both approaches have their benefit treatments should be evaluated in both before they are developed for use in humans. Transectic animal injury model, whereas contusion represents the typical injury mechanism in humans. A segments, which greatly exceeds the extent of neuronal damage in the transected spinal cord. Al loss of alpha-motoneurons and roots associated with spinal cord contusion is little addressed in Vertical target 4), it has direct implications for rehabilitation strategies and functional outcome. for degradation of neuronal function below the level of lesion in chronic, complete SCI.[38] The r regeneration-inducing therapy needs to be evaluated. In addition, the prerequisites to facilitate regenerating tract fibres and to maintain neuronal function in the postacute stage have still to b

Table 8 - Horizontal capability 1: Animal models.



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Although the majority of SCI studies to date have involved rats, genomic approaches are carried the development of a mouse model of SCI had priority in the 2nd ISRT strategy document.[2] No of knockout and transgenic mice is likely to provide insights into the molecular components of S

In each laboratory species used, the requirements of an animal model are that it is quantitative, permanent records that are open and available to other researchers. The results obtained with a reproducible when used independently by other research teams.

Ideally, experiments should have a sequential design that includes:

- Longitudinal observation of the behaviour in normal animals to establish the level of varia stabilise learning curves.
- Longitudinal observations of the same parameters after lesion to establish the degree of va the natural history and evolution of postlesional changes that occur without any intervent
- The therapeutic intervention should be applied only when the postlesional situation is stal assessment carried out as above.
- Variation must be related to the normal population variation. Postlesional variation shoul because animals cannot be assumed to be uniform, and correlation with the lesion histolo and location of the lesions that are associated with specific effects. In addition, posttherap individual variation in histological parameters of recovery (eg number of fibres regenerati should give valuable additional information.

Horizontal capability 2

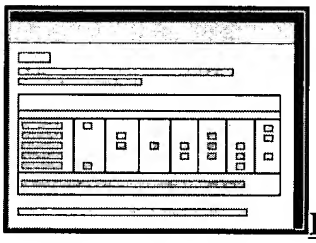
Developing methods to measure regrowth and restoration of function

The ability to determine accurately the extent of anatomical regeneration, physiological connect crucial for identifying a successful repair strategy. The current lack of reliable assessments of th spontaneous and treatment-induced recovery in laboratory animals and humans are fundament and potential clinical trials for SCI (see Vertical target 4).

The American Spinal Injuries Association (ASIA) score is not always fully reliable. For example, workers[67, 68] demonstrate that some patients who are classified as ASIA A (complete SCI) can EMG with pudendo-anal reflex (PAR). This sacral reflex is modulated by either voluntary or sup measure of spinal cord injury.[69] Measuring improvements in the PAR and similar systems migl progressive, postinjury changes in function, and outcome measures for future interventional tre

Methods to detect the partial preservation of long fibre tracts are also needed because present te unable to detect subtle neurological improvements. Assessments that reflect the whole clinical p spasticity, are also needed (**Table 9**). Although spasticity is useful for some abilities such as tra functional outcome for the patient.

Table 9 - Horizontal capability 2: Developing methods for measuring regrowth and



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To some extent neurophysiological and functional assessments can differentiate between the co compensation, neuronal plasticity and regeneration to improvement of function following SCI.[7] in particular, should give information about the impact of any new interventional therapy on th and of the peripheral nervous system.

Most patients recover significant function without intervention, and deterioration of SCI patien uncommon.[71] For example, most quadriplegic patients recover one spinal level of motor functic SCI, it is difficult to predict the preservation of discrete longitudinal fibre tracts and the likeliho of sensory and motor function. Difficulty in distinguishing between post-treatment improvemer might occur without intervention creates potential problems for interpreting the results of clinic new techniques are needed to assess more effectively spinal cord tissue that is spared after clini and to predict accurately any spontaneous recovery of function[37] (**Table 9**). Collection at multi physiological data mapping the natural history of changes in function in the period immediately

Imaging the site of injury, for example, by MRI can indicate continuity across a lesion but does n functional. Currently, electrophysiological assessments of sensory and motor tract function (eg s indicate the presence of large, myelinated fibres in the dorsal columns but not finer fibres in, fo and recovering or remyelinating fibres. Therefore, ways to identify different fibre tracts are neec electrodes, which recognise unique patterns of activity in discrete fibre tracts. Functional imagi

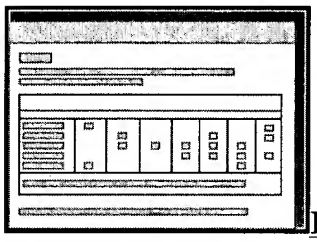
developed, and it is likely that the combination of functional imaging with selective stimulation pathways through, for example, contact-heat-evoked-potential stimulation of C and A delta fibr analysis of baseline and functional improvements from interventions.

Horizontal capability 3

Clinical trials

The many issues that surround optimisation of Clinical Trials of SCI treatments were discussed Clinical Trials Workshop on SCI.[73] Many SCI and other relevant (eg regulatory) communities w standards and guidelines for valid clinical trials could be developed and broadly accepted. One c establishment of a working group to bring forward detailed guidelines on how to develop clinica effective manner. Clearly, several of the issues relate to the adequacy of the animal model that is launch a clinical trial[74] (**Table 10** and Horizontal capability 1).

Table 10 - Horizontal capability 3: Clinical trials.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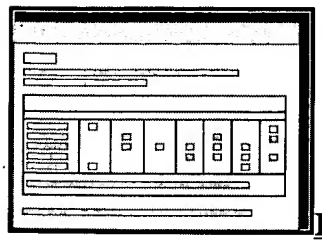
As a more general consideration, Research Governance applies to all who fund research propos research, and host research in their organisation. This is the process that sets standards and def these, requires monitoring and assessment, and improves research quality and safeguards the p scientific quality, promoting good practice, and preventing poor performance and misconduct. highest clinical standards, ISRT must ensure that its governance structures are appropriate to a Strategy.

Horizontal capability 4

Promoting collaborative research

The complexity of SCI in humans is such that multidisciplinary approaches are needed to under therapies to treat it. It is generally accepted that there is a need to continue to improve commun involved in spinal cord injury research. Therefore, ISRT regards collaboration as one of the keys To this end, it encourages collaborations between the researchers it funds, both clinical and bas

Table 11 - Horizontal capability 4: Promoting collaborative research.


Full table

It is important for scientists to understand the general and specific problems associated with SC might be necessary to foster the training and career progression of a new 'breed' of clinical scier clinical trials in SCI. Such individuals should be familiar with basic science and have clinical kn the design, execution and evaluation of clinical trials. They should also be able to evaluate resea of SCI patients and other clinicians. This is important because what might appear to be an excit might have limited potential for translation to the clinic because of gaps in understanding betw clinicians.

A single centre where different experts, such as basic and clinical scientists and clinicians who t probably most effective. From such a hub, a spoke organisation should be established to exchan compounds with other units, and to coordinate with other centres to enable sufficient patients t time.

In addition, collaboration between basic researchers and clinicians should help to evaluate the c complete SCI and, consequently, to better understand neuronal plasticity and degradation. This the different factors in determining the severity of functional loss after SCI, such as demyelinati site, and link them to therapeutic approaches. An example might be the maintenance of neuron specific, early-onset, functional training.[75, 76]

Contacts or collaborations outside SCI research should also be encouraged to make use of existi treatments and to ensure that mistakes are not repeated. For example, knowledge on the use of more advanced in other areas of research such as haematology and cardiology, and this should l

Collaborations with industry should be encouraged, both for support and as a source of new dru as a means of promoting international meetings where a wide spectrum of different aspects of S

Conclusions

This latest Research Strategy from the ISRT builds on the previously published strategies[1, 2] by recent advances in basic and clinical research that are relevant to restoration of function followi experience, identifying individual themes of basic and clinical research enables ISRT to focus re areas that would benefit from particular attention, and targeting specific research areas in this v maximising the effects of the available funding. As a research-based charity, ISRT intends grant directly by the themes described in this strategy document. However, this is not to say that othe considered should there be sufficiently strong evidence of their potential.

In keeping with the policy of promoting debate between all interested parties, another purpose Strategy is to stimulate discussion of the relative merits of the themes and approaches that are c deliberately wide-ranging and inclusive with respect to the themes described, and individual vie these approaches are likely to differ. By promoting this discussion, ISRT hopes to encourage del patients and other interest groups about the many issues that are involved in developing and va therapeutic advances in the near future.

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Spinal Cord

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Gene therapy for spinal cord injury and disease [In Process Citation]

Selected

J Spinal Cord Med 2002 Spring;25(1):2-9 (ISSN: 1079-0268)

Poulsen DJ; Harrop JS; During MJ
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An incomplete understanding of the pathological processes involved in neurodegeneration and dysfunction of spinal cord injuries and diseases makes these disorders difficult to treat. Repair of damaged or genetically impaired spinal cord also has been limited by the complexity, cellular heterogeneity, and relative inaccessibility of the tissue. Thus, therapeutic options for the treatment of either chronic spinal cord diseases such as amyotrophic lateral sclerosis or acute spinal cord injuries have been rather limited. Potential new therapeutic targets are being identified as our understanding of the molecular pathology involved in neural injury and regeneration increases. Recent advances in gene transfer techniques have made gene therapy a more realistic and viable strategy for the treatment of a broad range of spinal cord disorders. This review summarizes the current state of knowledge regarding the limitations and recent advances in gene therapy and potential application of this technology toward spinal cord injury and disease.

[This message was edited by Wise Young on May 04, 2002 at 12:09 PM.]

Wise Young 04-24-2002, 03:36 PM

Max, if you post articles or abstracts... can you enter a brief description and why you want to post it in the header, and the actual article with the URL address to the body of the message? Thanks. Wise.

perry 04-24-2002, 04:09 PM

i have just heard the same thing from a person at the reeve's foundation. the primates studies will lead the way.
gene therapy has been around for over 25 years, and now beginning to show success in animals. max,dr.wise how can we find out more.....

perry

Wise Young 04-25-2002, 10:02 AM

Perry, in spinal cord injury, there are two issues. The first is identification of beneficial (and deleterious) gene expression that can and should be manipulated in order to improve recovery, regeneration, remyelination. There are currently many laboratories systematically studying animal spinal cord injury models to identify regeneration-associated genes (RAGs), pain-associated genes (PAGs), neuroprotection-associated genes (NAGs), myelination-associated genes (MAGs), etc. Once identified, the expression of these genes can then be boosted or blocked in the spinal cord.

The second issue is the mechanism of changing gene expression. Gene therapy today is being carried out in several ways:
• Transgenic - the genes of an egg or sperm are modified and the subsequent organism then has a knockout (deleted), knockin (inserted), or dominant negative (an interfering gene) added. This is currently not an option for adult.
• In vivo transfection - the gene is inserted into certain cells by virus, liposomes, or other vectors. The viral

method is the most efficient and popular at the present but got into trouble recently, particularly adenovirus (the common cold virus), because it initiated fatal inflammation in one patient (Jesse Gelsinger). Many companies have touted other non-viral means of inserting genes that are generally less efficient but presumably safer.
• Ex vivo transfection and implantation of transfected cell - specifically cells can be removed from the body, transfected so that they express certain gene products, and then implanted back into the body. Actually, the first use of this technology in the CNS was for spinal cord injury (Tuszynski, et al.)

An alternative and growing approach to manipulating gene expression is with drugs. A large number of drugs and factors are known to turn off and on certain genes. For example, the tetracycline antibiotics are known to turn on certain genes. Likewise, there are many so-called nuclear factors that go into a cell and turn on genes, i.e. NF-kappa B is the factor that turns on inflammatory genes.

There is really no magic about gene expression. We just have much more powerful tools that allow us to measure and manipulate gene expression. So, once we know which genes we want to turn on and which to turn off or modulate, it can and will be done. Unfortunately, as a recent report in the Wall Street Journal suggests, the human genome project has not yielded a huge number of treatments for the pharmaceutical industry.

Despite massive investments, the number of drugs that have been approved by the FDA has fallen in the past three years compared to previous years. The reason is that people were expecting knowledge of the human gene to produce new drugs. They had not realized that the knowledge has produced the possibility of many drugs but the same amount of work and information must be gathered about each candidate drug before it can be successfully taken to clinical trial. Thus, the investment did not reduce the expense or time in developing the drugs. It just increased the number of potential drug candidates.

One of the most interesting outcomes of the human genome project is that is has shown us how similar humans are to other animals. I suspect that primate experiments will not be essential for moving all therapies into clinical trials. Scientists are working very hard to develop surrogate measures, using human cell cultures (stem cells, etc.) that allow testing of therapies without doing as many large animal experiments. Of course, the FDA continues to require large animal safety (toxicity) studies before clinical trial but every effort is being made to reduce the number of animals required.

Wise.

Note: Performing your original search, ***ex vivo spinal cord injury*** , in PubMed will retrieve ***38*** citations.

1: Clin Neurosci. 1995-1996;3(5):268-74.

Links

Ex vivo gene therapy for Alzheimer's disease and spinal cord injury.

Blesch A, **Tuszynski M**.

Department of Neurosciences-0608, University of California-San Diego, La Jolla 92093-0608, USA.

Gene transfer is a potential means of treating chronic neurologic disorders and injury related neural degeneration. One approach for transferring genes to the CNS is to genetically modify cells in vitro and then transplant the cells to the CNS. For example, fibroblasts can be infected with a replication-defective retrovirus expressing a transgene, and can then be transplanted into the brain or spinal cord, thereby providing neurotrophic factors and substrates for axonal growth and elongation. In this review we discuss the grafting of neurotrophic factor secreting autologous fibroblasts in the rat and primate CNS. NGF secreting grafts have been shown to prevent degeneration of cholinergic neurons in the basal forebrain of primates and to induce sprouting of sensory, motor, and noradrenergic neurites after spinal cord injury. These results suggest the potential usefulness of ex vivo gene transfer for the treatment of Alzheimer's disease and spinal cord injury.

PMID: 8914793 [PubMed - indexed for MEDLINE]

Reviews

Nature Reviews Neuroscience 7, 628-643 (August 2006) | doi:10.1038/nrn1955

There is a **Corrigendum (1 November 2006)** associated with this article.

Focus on: **Nerve regeneration**

Therapeutic interventions after spinal cord injury

Sandrine Thuret[1,4], Lawrence D. F. Moon[2,4] and Fred H. Gage[3] About the authors

Abstract

Spinal cord injury (SCI) can lead to paraplegia or quadriplegia. Although there are no fully resto rehabilitative, cellular and molecular therapies have been tested in animal models. Many of thes clinical trials. Here, we review these potential therapies, with an emphasis on the need for repro efficacy. Individual therapies are unlikely to provide a panacea. Rather, we predict that combina

improvements in outcome after SCI. Basic scientific research should provide a rational basis for clinical therapies to different types of SCI.

- View **At a Glance**

Worldwide, an estimated 2.5 million people live with spinal cord injury (SCI), with more than 1; year (see **International Campaign for Cures of Spinal Cord Injury Paralysis** in Online restorative therapies for SCI as yet and so prevention (for example, effective seat belts, weapons the best medicine (see **Foundation for Spinal Cord Injury Prevention, Care and Cure** i significant impact on quality of life, life expectancy and economic burden, with considerable cos loss of income. In one study, quadriplegics ranked recovery of arm and hand function as a prior recovery of sexual function as most important (when measured against recovery of bladder/bow **autonomic dysreflexia**, improving walking movements and trunk stability, regaining normal pain)[1]. Therapies addressing these and other important priorities (such as recovery of cardiovas skeletomuscular properties, and reducing spasticity) have been reviewed elsewhere[2, 3, 4, 5, 6]. I limb function, which is the focus of most ongoing animal studies and clinical trials for treatmen

To identify therapies that are unambiguously safe and effective, the scientific and clinical SCI cc that preclinical studies be reproduced by independent laboratories, and that clinical trials have include an a priori unambiguous definition of primary outcome measures and any intended stra methods that are sensitive enough to detect potentially small increments in function[7, 8, 9]. Seve evaluated independently under contractual arrangements between the National Institute of Neu (NINDS) and several Facilities of Research Excellence for SCI (FORE-SCI; see NINDS Facilities Cord Injury in Online links box), including the Miami Project to Cure Paralysis and the Reeve–I information on clinical trials, readers are directed to governmental and international consensus how US Food and Drug Administration regulatory processes relate to the standing of one SCI di **translating promising strategies for spinal cord injury therapy** in Online links box)[10].

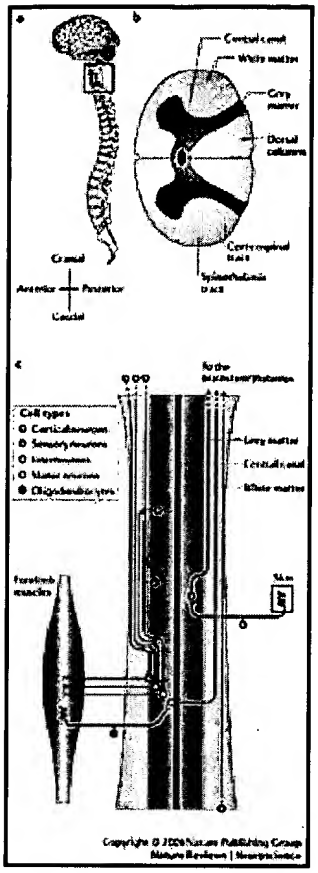
Here, we stress various cellular and molecular strategies that are supported by more than one p and that result in functional improvements after SCI; many of these strategies have reached, or of the potential therapies described below might produce only small improvements, and a comb needed to improve everyday quality of life. Speciality journals and general audience media need the safety and efficacy of potential therapies to avoid raising and then dashing the hopes of thos government, those carrying out research, or the general public.

Endogenous response to SCI

The normal architecture of the human spinal cord (**Fig. 1**) can be radically disrupted by injury. outcome[13, 14] and can result from contusion, compression, penetration or maceration of the sp cells, including neurons, oligodendrocytes, astrocytes and precursor cells[15] (**Fig. 2**), and any re interrupt descending and ascending axonal tracts, although circumferential white matter is ofte the spinal cord, additional structure and function are lost through active secondary processes (f oligodendrocytes and loss of myelin[16]). Demyelinated axons are observed up to a decade after h which these axons survive unmyelinated or become remyelinated by central or peripheral myeli investigation[18]. Resident and invading inflammatory cells (including neutrophils, microglia, ma range of destructive and reparative roles[19]. SCI culminates in glial scarring, a multifactorial pro astrocytes, glial progenitors, microglia and macrophages[20, 21], fibroblasts and Schwann cells[17,

perpendicular to the neuraxis and appears impenetrable. The scar also contains secreted and tra of axon growth[23, 24]. Progressive expansion of the injury across more than one segment (syring months or years, sometimes proving fatal.

Figure 1 | Intact spinal cord.



a | Schematic showing a sagittal view through the human CNS. b | Transverse section through h relationship between axonal tracts and grey matter. c | Cortical, brainstem and spinal axons pro grey matter, which in turn send axons through the PNS to target organs, including muscle. Prim through the PNS to second order sensory neurons in the CNS grey matter, which, in turn, send a dorsal columns to supraspinal regions. Oligodendrocytes myelinate ascending and descending a

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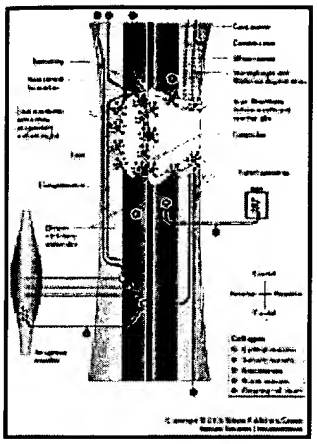
Figure 2 | Spinal cord after injury.



Schematic showing a sagittal view through a region of cervical spinal cord injury (SCI), depictin different types of injury. Many cells die immediately, as well as progressively, after SCI. Cysts us After penetrating injury, cells from the PNS often invade the injury site to form a connective tiss progenitor cells and microglia. Many ascending and descending axons are interrupted and fail t Some axons form new circuits with motor neurons via interneurons. At the site of cyst formatio that are formed from ependymal cells. Disconnected myelinated axon segments are phagocytos spontaneous remyelination occurs, largely by PNS Schwann cells, whereas denervated (non-spa

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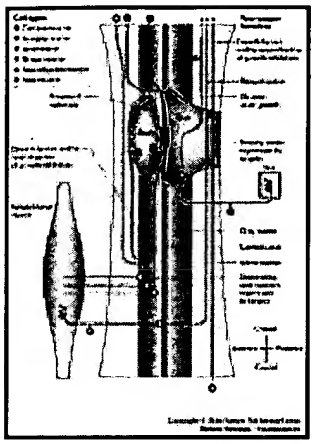
In contrast to these destructive events, commonly observed pathological features do indicate so (**Fig. 2**). Whereas there is little or no neurogenesis in the injured spinal cord, proliferation in th canal generates new precursor cells that exclusively differentiate into glial cells[15, 26, 27, 28]. Lin lesions might even be spanned by **trabeculae** containing axon sprouts[25, 29]. Sprouting is large molecular factors[24, 30], and few axons regenerate over long distances back to their original targ cortical, brainstem and spinal **plasticity** occur that could contribute to limited compensatory r circuits can bypass the lesion, including sprouting of injured corticospinal axons onto spared, lo that increase connectivity with lumbar motor neurons[33, 34]. Cortical sensorimotor areas can fu the subcortical level, the rubrospinal system can reorganize and compensate for much of the fur injury[31].

Therefore, although there is some spontaneous repair after CNS injury, it is incomplete. Furthe combination of effective and safe therapeutic interventions (**Fig. 3**).

Figure 3 | Injured spinal cord after combination treatments.



Schematic showing a sagittal view through injured cervical spinal cord after a hypothetical coml are filled by vascularized grafts and trabeculae are spared. Grafts provide remyelinating cells, ar regions and in intact spinal cord are neutralized using antibodies, peptides or enzymes. Grafted relay circuits or the regeneration of injured axons back to their original targets. Furthermore, re synapses to be stabilized and reverses muscle atrophy.

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Cellular therapeutic interventions

Cellular transplantation after SCI has several aims: to bridge any cysts or cavities; to replace dea neurons or myelinating cells); and to create a favourable environment for axon regeneration.

Transplantation of peripheral nerve. After SCI in adult rats, **autologous transplants** (support ingrowth of various axonal types but not supraspinal axons[35]. Peripheral nerve grafts v therapies (including anti-inflammatory drugs, vertebral wiring, fibrin glue and acidic fibroblast with regeneration of supraspinal axons into, through and beyond grafts[36, 37, 38, 39].

A similar strategy has been tested in non-human primates after lateral spinal hemisection[40]. N detected but some spinal axons were found to have regenerated 4 months after injury. This appı chronic, incomplete human SCI, with one peer-reviewed report of limited functional recovery ir control patients were investigated[41]. Anecdotally, this strategy has not proved successful in peo much work remains to be done to determine whether therapies that involve peripheral nerve br effectively improve outcome after human SCI.

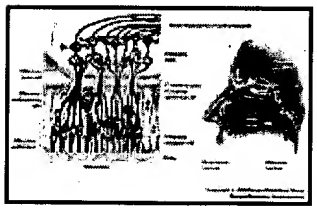
Transplantation of Schwann cells. Schwann cells from peripheral nerves have been trans either being injected as suspensions after contusion injury[42] or implanted into channels contai hemisection[43] or complete transection[44]. After transection and implantation of Schwann cells, bodies near the grafts extend into these bridge grafts, become myelinated[44] and are electrophys axons do not leave grafts distally to reinnervate the host. After contusion and implantation of Sc and sensory and spinal axons extend into grafts, and many are remyelinated[42]. Recovery of hin

some[42], but not all[46], studies. Consequently, combination therapies have been evaluated. After regeneration of CNS axons beyond bridges has been reported in response to transplantation of ; delivery of neurotrophins[47, 48], a steroid (methylprednisolone sodium succinate)[49] or olfactor

Human Schwann cells have also been transplanted into the transected spinal cord of rats with a rats, brainstem axons regenerated into grafts and spinal axons regenerated distal to grafts. Fun reported, although weight-supported stepping was observed in only one rat[51]. Finding the most combination therapy involving Schwann cells remains crucial. One important step towards hum safety and efficacy of transplanting autologous Schwann cells into non-human primates after co been no peer-reviewed reports of clinical trials involving the transplantation of Schwann cells a

Transplantation of olfactory nervous system cells. Cells from the embryonic and adult have been transplanted after SCI. Indeed, porcine, primate and human cells are now being teste models of SCI and demyelination[53, 54, 55, 56, 57]. Functional recovery and/or CNS axon regene olfactory nervous system-derived cells are transplanted immediately or up to 2 months after SC [64, 65]. After lateral cervical hemisection in adult rats, injection of cells from the olfactory bulb l function and enhanced performance on a climbing task[58]. These transplants might also prevent may enhance myelination after SCI[68], although whether OEG directly myelinate axons after SC Transplants of cells from the olfactory nervous system do not, however, promote CNS axon rege under all circumstances[42, 67, 70, 71]. FORE-SCI re-assessment of delayed transplantation of **olf** transection of adult rat spinal cord failed to find any improvement in hindlimb function, althou found in caudal spinal cord tissue[72].

Figure 4 | The olfactory nervous system.



Schematic of a sagittal section through the human head, showing the olfactory nervous system (nervous system depicted in greater detail (inset). Stem cells at the base of the olfactory epitheliu neurons throughout life, which extend axons de novo to the olfactory bulb. These axons are wra as they pass through the lamina propria from olfactory mucosa and into the CNS via the cribrifc permission, from Ref. 275 © (1996) TM Higher Education Group.

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Transplants of cells derived from fetal olfactory bulbs or the adult mucosa have reportedly alrea 400 humans in China, Portugal and Colombia[8, 73, 74]. Many procedures do not meet internatio and, because controls are not included and comprehensive follow-up studies have not been perf safety and efficacy of this intervention, although there are reports of improvements in motor an

independent case report describes rapid segmental improvement in a single patient classified as according to the American Spinal Injury Association (ASIA) Impairment Scale (**Box 1**) — who n quadriplegic[75]. An additional seven patients have been independently assessed pre- and post-o (including meningitis), and no clinically useful improvements, being observed. The view was ex recommend this procedure to patients[74].

Box 1 | The ASIA Impairment Scale

- **Full box**

Elsewhere, formal veterinary and human clinical trials using cells derived from the adult olfactc advancing. SCI in dogs often occurs as a result of road traffic accidents or intravertebral disc ext to test potential therapeutics in a large, heterogeneous patient population with variable injury s bulb have been transplanted autologously into nine dogs after naturally occurring thoracolumb events up to 2 years later[76]. Some hindlimb function was recovered (including weight-supporte note, controls and blind testing are required in future trials.

In one **Phase I clinical trial** in humans, cells were collected from the adult human lamina prc into the spinal cord of three patients with thoracic injuries that had occurred at least 6 months controls were included. No adverse consequences were reported in these patients after 1 year, al used for neurological assessment were reported: a 3-year follow-up study is planned. A large nu and sensitive testing will be required to rule out the possibility that functional tissue has been d complete patients, particularly before applying this therapy to incomplete injuries.

It is necessary to establish whether there are conditions under which transplantation of cells fro works reproducibly to promote plasticity, regeneration, remyelination, neuroprotection and/or issues to be resolved include the optimal source of cells (lamina propria versus olfactory bulb), and graft strategy (for example, injection of suspensions or transfer within cellular matrix). It w whether enriching cultures for specific phenotypes of cells improves outcome[58, 69, 78, 79].

Transplantation of embryonic CNS tissue. After spinal cord transection in animal model cord into the lesion site, a small number of host axons regenerate into the transplant but termin border[80, 81]. Small but significant functional recovery is observed in rats[82, 83] and cats[84]. This distance growth into, through and beyond grafts, and the authors suggest that it is instead caus relays, affording transmission of signals via transplanted neurons, which are innervated by pro turn to distal host neurons. Grafts might also provide growth factors or improve conduction in s spinal cord transplants are combined with neurotrophin delivery after complete spinal cord tra function is observed[87], with some supraspinal and propriospinal axons growing into the caudal

Intraspinal transplantation of fetal spinal cord has been tested in a clinical trial involving patier complications were observed and cysts were obliterated in all the patients. These trials have not standard treatment for SCI or syringomyelia[7], perhaps because of the difficulties associated wit transplantation.

Transplantation of embryonic stem/progenitor cells. Multipotent progenitor cells can and stem cells can self-renew indefinitely and differentiate into any cell type. Three of the majo repair after SCI are controlling the survival, integration and differentiation of transplanted cells

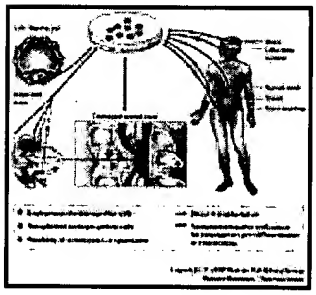
functional recovery by reconstituting damaged circuits, remyelinating axons, and increasing pla
Many groups have studied the fate of stem cells[91, 92] or progenitor cells[93, 94, 95, 96, 97, 98, 99]
embryonic CNS or human umbilical cord blood and transplanted into the injured adult rodent s
reported modest improvements in functional recovery[91, 100, 101].

The potential of human fetal stem cells in animal models of SCI is currently being investigated.
human fetuses have been transplanted into immunosuppressed mice[102] and non-human prima
cases, the transplanted cells survived and differentiated into cells with characteristics of oligode
associated with locomotor improvements[102, 103].

The most recent successful approach with embryonic CNS-derived stem/progenitor cells is to u
pre-differentiated to a desired lineage before transplantation. Transplantation in rats of neuron
contusion injury improved bladder and motor function. The cells survived, filled the lesion site,
some characteristics of neurons and glia, resulting in sparing/sprouting of descending pathway
embryonic stem cell (ESC)-derived oligodendrocyte-restricted progenitor cells into the adult rat
enhanced remyelination and promoted improvement of motor function. The cells survived, mig
differentiated into oligodendrocytes. By contrast, when cells were transplanted 10 months after
remyelination or locomotor recovery[105, 106]. This study is being considered for FORE-SCI repl
Cure Paralysis (see Online links box).

Transplantation of adult stem/progenitor cells. Adult stem cells are now being conside
contrast to ESC transplantation, adult stem cell transplantation should reduce ethical concerns
should not be rejected. Various adult progenitor cells have been implanted in rodent models of
olfactory system (see above) to bone marrow-derived stem cells, cultured spinal cord and brain
cells[107] (**Fig. 5**).

Figure 5 | Potential sources of stem/progenitor cells for transplantation into the ir



Stem/progenitor cells can be collected at three different stages of development: from the inner
blastocyst; from the brain, spinal cord, olfactory system or umbilical cord of the fetus; and from
system, bone marrow or blood of the adult. Each of these cell populations can be propagated in
produce a molecule of interest, or be restricted to a particular cell fate before transplantation in
these cells (those of fetal CNS origin and umbilical cord blood cells) could eventually be transpl
Some of these cells have the potential to be used for autologous transplantation, including cells
umbilical cord blood cells (which can be frozen at birth for use in later life), haematopoietic ster
cells. Also, endogenous stem/progenitor cells are present at the injury site and are actively divid
and fate might provide an alternative to transplantation. This diagram is based on published da
[95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 108, 109, 110, 111, 113, 114, 115, 116, 117, 118, 119, 120,

transplantation after SCI in animals.

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Box 2 | Ethics of spinal cord injury research and clinical trials

- **Full box**

Adult bone marrow contains several different stem cell populations, including haematopoietic s stromal cells (BMSCs), also known as mesenchymal stem cells (**Box 3**). Transplantation of HSC after compression-induced SCI in mice[108, 109] and transplantation of BMSCs significantly imp mice and rats[109, 110, 111]. However, the potential mechanisms by which BMSCs act are currentl and axonal elongation-facilitating actions have been proposed[110]. Also, the functional outcome caution because many are primarily based on one evaluation protocol without other behavioura A small-scale human trial was conducted in which autologous BMSCs were intravenously delive improvements observed appeared to fall within an expected range of spontaneous recovery, and ASIA category B to D. Nevertheless, without controls or some indication of cell viability within t that a measure of procedural safety was demonstrated. To our knowledge, peer-reviewed result study[8].

Box 3 | Bone marrow cells

- **Full box**

Adult neural progenitor cells (NPCs), isolated from the dentate gyrus, the subventricular zone o self-renew, and to be multipotent in vitro and after transplantation into the CNS[112, 113]. After t the intact and injured murine spinal cord, differentiation into only astrocytes or oligodendrocyt mouse brain-derived adult NPCs were transplanted into the injured spinal cord of adult rats. Th growth factors to selectively increase the number of oligodendrocyte precursors after transplant post-injury survived, migrated, integrated in the injured spinal cord tissue, generated mature ol the injured axons, and promoted some functional recovery. However, NPCs transplanted 8 wee failed to exert similar effects[117]. Therefore, there is a need to find and neutralize the inhibitory interfere with NPC survival after transplantation.

Adult neural stem cells also reside in the spinal cord[118], and the ability to regulate their numbe provide an alternative to transplantation. To regulate their numbers and fate to promote recove which molecules are involved in governing neural stem cell proliferation, migration and differe endogenous stem cells would require no exogenous stem cell sources and would therefore circu rejection, as well as the ethical and moral considerations associated with their use.

Transplantation of engineered stem/progenitor cells. The injured adult spinal cord is survival, neuronal differentiation and maturation. Therefore, to enhance the capacity of stem ce recently begun to engineer stem cells to have better survival, and desired differentiation and ma attempt to increase the survival of transplanted rat ESCs, ESCs were genetically modified to ove

protein. This led to tumour-like growth of cells, accompanied by increased morbidity and morta transplanted in the compressed mouse spinal cord, engineered mouse ESCs expressing the cell : longer and migrated rostrally and caudally from the lesion. Corticospinal axons showed interdig and extended into and, in some cases, beyond the lesion site[120].

It is apparent that transplantation alone of stem/progenitor cells after SCI will not lead to optin will be necessary for optimum return of function. Advances in molecular biology (for example, v manipulation of these cells to express molecules of interest[121, 122]. These types of combination further development and careful animal testing, individually and jointly, before any clinical tria

Transplantation of activated macrophages. It has been suggested that the failure of the attributed to the nature of the macrophage response[123], which differs from that observed in the of hindlimb function has been reported after transection and transplantation of activated macrc with PNS or skin tissue. Fibres were shown to extend through the lesion, and re-transection of t previously recovered functions[124, 125]. However, the degree of recovery was comparable to that cell types and occurred only in a subgroup of rats[126].

By contrast, activation of intrinsic macrophages at the spinal contusion site with micro-injectio negative effects on hindlimb functional recovery and tissue survival[127]. Depletion of macropha better hindlimb usage during overground locomotion, more extensive white matter sparing and

There is, therefore, evidence that macrophages have deleterious effects on functional recovery, a would be advantageous to replicate these studies in independent laboratories. Moreover, no pee transplantation of activated macrophages in non-human primates have been described.

Proneuron sponsored Phase I clinical trials on the transplantation of activated macrophages in and Belgium (see **Proneuron** in Online links box). Blood-derived monocytes activated using b eight ASIA category A participants between 9 and 14 days after injury. No irresolvable adverse e participants improved to ASIA category C, which was claimed to be well above the expected rate multicentre, randomized controlled, **Phase II clinical trial** for ASIA category A participants i and Israel, but recruitment for this clinical trial has currently been suspended for financial reas communication).

Molecular therapeutic interventions

Molecular therapies after SCI have several aims: to protect neurons from secondary cell death; t enhance conduction.

Neuroprotective therapies. Substantial effort has been devoted to limiting the evolution of development of neuroprotective measures for acute SCI (and, potentially, for accompanying sur [130]. Delivery of antibodies against a cell adhesion molecule present on neutrophils and monocy damage after SCI in rats and improves motor function while reducing both autonomic dysreflex Erythropoietin has been reported to improve outcome[130], although this finding might not be re **Cure Paralysis** in Online links box). Several studies have also recently reported that intravenc and improves hindlimb function in mouse and rat models of SCI[132, 133, 134], and this commonl clinical trials for SCI[9].

Intravenous steroids (for example, methylprednisolone sodium succinate; MP) have been regist many countries[135]. There is considerable debate as to whether MP has been proved to be safe a [137, 138, 139, 140]. Treatment is claimed, controversially, to be beneficial if an appropriate regim type of injury and whether more than 3 or 8 hours have elapsed since incurring the injury; how treatment, incorrect dosing or treatment of penetrating SCI has been shown to be detrimental[1 randomized trials examined whether modest improvements have been shown using MP, GM-1 g hormone (TRH), nimopidine and the NMDA (N-methyl-D-aspartate) antagonist gacyclidine[8]. T trials, primary outcome measures were not significant and placebo controls were lacking. When observed, these were often based on post hoc stratification, and severe side effects were also rep trials of neuroprotective agents have shown that large multi-centre, double-blind studies for SC placebo-controlled **Phase III clinical trials**, with primary outcomes clearly recorded a priori, highly effective and safe neuroprotective therapies for human SCI[10, 11].

Enhancing conduction. Electrophysiological studies of humans with chronic SCI indicate th demyelination and that only a proportion become remyelinated (although denuded axons migh remyelination (by host or transplanted glia) or enhance conduction could yet prove useful. A po aminopyridine) that can improve axonal conduction has been tested in several double-blind, pla with chronic SCI[17]. However, Acorda Therapeutics' Phase III clinical trials of an oral, sustained aminopyridine showed a trend for improvements only in spasticity (see **Acorda Therapeutic**

Delivery of growth factors. Growth factors modulate neuronal survival, neurite outgrowth, neurotransmission. Exogenous administration of growth factors has been proposed as one pote The effectiveness of this approach has been tested using, for example, brain-derived neurotroph [145, 146, 147], basic fibroblast growth factor[148], glial cell-derived neurotrophic factor (GDNF)[14 [144, 150], and neurotrophin 3 (NT3)[141, 145, 146, 151, 152], NT4 and NT5 (Ref. 153). Growth facto spinal cord by transient injection[154], continuous infusion[143, 144] or insertion of an artificial ca factors[142]. Ex vivo gene therapy involves grafting cells, usually fibroblasts, that have been trans growth factors[145, 146, 151, 152, 153]. In vivo delivery of growth factors has also been achieved us adenovirus[155, 156], adeno-associated virus (AAV) and lentivirus[157] (see below).

After SCI, the exogenous delivery of NGF in rats can induce growth of coerulospinal axons[158, 1 corticospinal axons[160]. BDNF induces recovery of forelimb function after cervical lateral hemis rubrospinal, reticulospinal, vestibulospinal, raphespinal, and local sensory and motor axons[161, and BDNF improves bladder and hindlimb function after a mid-thoracic contusion[152], and GDI dorsal column sensory axons after partial and complete spinal cord transections and induces re delivery of growth factors alone leads to only partial recovery, researchers are now combining th factors with other therapeutic approaches: OEG transplants and NT3 (Ref. 67); marrow stroma exercise with serotonergic agonists and NT3 (Ref. 166). In addition, delayed delivery of growth acute delivery because axons of chronically injured neurons can lack appropriate growth factor

Unfortunately, clinical trials using systemic delivery of growth factors for various disorders hav efficacy or unacceptable side effects, or both[168]. Obviously, to avoid adverse effects, growth fact quantities to have an effect but their distribution must be restricted to the site at which they are vivo NGF gene delivery in patients with Alzheimer's disease by implanting autologous fibroblast human NGF in the forebrain showed promising results, with no side effects attributable to the d

of the rate of cognitive decline[169]. However, to move forward with the clinical application of gr further work is required to show whether this promotes CNS axon regeneration and leads to fur human primates.

Delivery of cAMP or small GTPases. Cyclic AMP (cAMP) can induce axonal sprouting of c and of injured adult rat spinal sensory neurons in vivo when prophylactically applied[171, 173, 17 therapy needs to be effective when applied after SCI. In zebrafish, post-injury application of cA CNS axons and restored function[175]. After injury, the CNS environment is more permissive for Therefore, elevating cAMP levels after SCI has been tried in combination with other treatments. locomotion were observed[176, 177] after delivery of Rolipram (which prevents the hydrolysis of c transplants[176], and after adminstration of the combination of Schwann cells, a cAMP analogue any human clinical tests can begin, therapeutic windows of delivery of cAMP analogues must be delivery established, ideally in contusion injury models in rodents or primates.

Other strategies targeting molecules that are intrinsic to neurons could be viable, with modulati approach. Many factors that limit axon regeneration (see below) signal to the neuronal cytoskel Rho and Rac[178, 179, 180]. Inhibition of Rho by a bacterial toxin, C3-ADP-ribosyltransferase, pr degree of functional recovery after dorsal hemisection injury in adult rats[181], although these re study[182]. Side effects have also been reported[182, 183] and, although potential explanations hav efficacy of small GTPase modulation need to be further evaluated before their use for human SC Therapeutic has developed a cell-permeable variant of a Rho inhibitor known as Cethrin (BA-21 multi-centre Phase I/IIa trial that will include ASIA category A patients who are scheduled to re days of thoracic SCI; Cethrin will be applied using fibrin[184] (see **BioAxone Therapeutic** in O

Rho kinase (ROCK) acts as a downstream effector of Rho[186]. Inhibition of ROCK by a peptide-l molecule inhibitors stimulated or accelerated functional recovery, and had a neuroprotective ef models when given locally or systemically immediately after injury either as a single dose or ove [188]. However, it should be kept in mind that ROCK inhibitors have teratogenic potential[189] an functions of small GTPases might reduce the therapeutic specificity of the compounds that mod

Modulation of interactions with myelin inhibitors. Intact and injured CNS myelin con molecules (including Nogo-A, myelin-associated glycoprotein, oligodendrocyte myelin glycopro ephrin B3)[190, 191, 192, 193]. Various therapies have been developed to target and overcome the delivery of anti-Nogo therapeutics, independent laboratories report CNS axon growth and reco [195, 196, 197, 198, 199], although not all[200, 201], rodent models of SCI, and report no nociceptive against Nogo-A have recently been shown to promote growth of corticospinal tract axons after t hemisection in four out of five marmoset monkeys tested[192]. Future experiments might show w improve outcome in contusion or compression models of SCI. Phase I clinical trials using huma in progress for ASIA category A patients with thoracic SCI in association with Novartis (M. Schw

Therapies targeting molecules in receptor complexes for Nogo-A[203] are also being tested. In so Nogo-A, Nogo receptor or NGF receptor leads to CNS axon growth and functional recovery[204, factors in the negative studies need to be elucidated because these could be important future ta delivery of **NgR(310)ecto-Fc** enhances corticospinal and raphespinal axon growth after dorsa rats and enhances electrophysiological and behavioural recovery[209, 210]. Delayed, subcutaneo

promotes growth of corticospinal axons and serotonergic fibres and a degree of locomotor recov hemisection[211, 212]: independent testing of NEP1–40 by one FORE-SCI centre is underway (see **Centre** in Online links box).

Extracellular matrix modifiers. Transient suppression of collagen synthesis promotes CN and, when combined with an analogue of cAMP, it has been reported to promote CNS axon rege after acute SCI[214] (but see Ref. **215** for a contrasting result). Neuraxo has reported its intention combination therapy, which they have designated Cordaneurin, in human SCI (see **Neuraxo B** links box). However, it would be valuable to reproduce these results independently, and to carry primates.

In adult rats, degradation of growth-inhibitory chondroitin sulphate by delivery of the bacterial (ChABC) promotes regeneration of injured CNS axons and recovery of function after dorsal colu spinal cord hemisection in adult rats, delivery of ChABC promotes regrowth of axons from spina nerve grafts[218] and regrowth of CNS axons into the spinal cord beyond hemichannel bridges co complete transection and implantation of channels containing Schwann cells, delivery of ChAB(serotonergic axons beyond grafts[220]. Intrathecal delivery of ChABC also promotes recovery of l following severe (although not moderate) thoracic contusion injury in adult rats[221]. Tests for ef human primate models of SCI remain to be reported. Seikagaku is testing ChABC in Phase II cli discs (see **Seikagaku Corporation** in Online links box), which could aid translation to treatm

Rehabilitative training

Improved locomotor function is often seen in mammals with incomplete and even complete SCI rehabilitation[222]. Locomotor training even enhances the ability of many spinally transected ma body-weight support is provided[31, 223, 224]. This improvement occurs because, after SCI, the sp does not become silent but maintains active and functional neuronal properties, and can respon the level of the injury. It can generate oscillating coordinated motor patterns and is capable of c Increasing numbers of animal experiments combine rehabilitation/physical therapy with other regeneration and recovery of limb function[228, 229, 230, 231].

Many SCI clinical trials that are currently recruiting participants or are already in progress addr including upper-extremity exercise, body-weight-supported treadmill training, robotic or manu **functional electrical stimulation** (FES) (see **Clinical Trials.gov** in Online links box)[2]. Su empirically which types of locomotor training and rehabilitation are optimal for recovery of fun locomotor training enhances the ability of humans with neurologically complete SCI to walk on weight support is provided[31, 223, 224], although rehabilitation does not yet enable patients with walk unassisted overground[233]. FES of the dorsal surface of the spinal cord can induce step-lik corresponding electromyographic activity in the leg muscles in patients with complete SCI[226]. A centre trial has shown that many patients with recent, incomplete SCI achieve independent wall either using conventional devices or using body-weight-supported treadmill training[234, 235]. P also benefit from treadmill or overground locomotor training: for example, improvements are s (although outside the testing environment, participants did not walk independently of their whe ASIA category C patient reported that a combination of treadmill training and spinal cord epidu quantity of stepping during the training session and resulted in an immediate improvement in t

superior to that obtained with only treadmill training[236]. Therefore, the combination of central peripherally (locomotor training) induced stepping appears to be an effective method for restor of normal supraspinal input and should be explored further. Improvements in health have also including improved cardiovascular performance and reductions in spasticity, bone loss and blac

The mechanisms by which physical therapy or rehabilitation improve function after SCI need to could allow for rational improvement in therapy. Experimentation is also vital to identify safe a exercise can pose special risks to people with SCI, including autonomic dysreflexia, fracture or r People with SCI have atypical physiological responses to exercise (for example, abnormal heart to sustain intense exercise[2]. Inappropriate exercise could also be detrimental after SCI[238, 239]. potential confounding factor in clinical trials because it is difficult to control, although we shoul without strong justification.

Despite the documented advantages of exercise and rehabilitation, a US survey of quadriplegics reported having no access to exercise, and a further ~45% reported having to exercise on their c physical therapist[1]. Therefore, much remains to be done politically to ensure that therapies that are made available to individuals with SCI.

Technical aspects

Translating cellular therapies to the clinic. Because autologous transplants of cells or ti immunosuppression to escape immune rejection, they represent an attractive therapeutic optio source for autologous grafts of peripheral nerves or Schwann cells because only a minor deficit i biopsy. The olfactory mucosa is more accessible than the olfactory bulb for autologous transpla autologous transplants using tissue from the olfactory bulb have been carried out in dogs[76]. Ex neurotrophins[54] or other mitogens[241] might be possible when the amount of tissue is limiting, proliferation after transplantation needs to be prevented[242].

Cellular suspensions can be transplanted into the acute, post-injury milieu or into irregularly sh later in the injured spinal cord. Tissue grafts (for example, peripheral nerve grafts) are perhaps shaped (for example, anatomically complete) injuries or for external routing (for example, direc routes of administration might include delivery of cells into the cerebrospinal fluid by lumbar p towards the injury and exert a beneficial effect by reducing injury size[243, 244]. Lumbar punctur its minimal invasiveness, simplicity and low cost.

Cells could also be genetically modified to deliver therapeutic molecules[145, 146, 151, 152, 153, 16 include fibroblasts, ESCs, neural stem/progenitor cells, OEG and Schwann cells. However, in m transplanted cells die after transplantation and are replaced by host cells[245, 246, 247]. Althoug might still confer benefits, ensuring survival of the cells and controlling regulation of expressio transgenic delivery. Identifying transplanted cells requires the use of a marker that neither indu transfers to host cells[246].

The protective or reparative potential of transplants of a given cell type can be established only l alternative cell types (rather than merely injections of fluid). With regard to complete injuries, c regardless of the cell type transplanted[126]; a goal for the future (currently elusive) will be to ena that supports body weight[226]. Finally, it might be short-sighted to select a cell type for a clinica

cell types within a single experiment. If the race to clinical trial results in one cell type becoming been evaluated against other cell types, then other (potentially better) cells might not be easily t difficult to deny a clinical trial participant a therapy that has already been shown to be partially case when evaluating potential drug alternatives to MP[138].

Translating molecular therapies to the clinic. Techniques to deliver molecular therapie intracerebroventricular, intrathecal and intraspinal injection, continuous infusion or insertion c molecule of interest. Viral vector-mediated transfer of molecules to the injured spinal cord is en strategy[157]. In vivo gene therapy has been tested in models of SCI using viruses, including herp lentivirus and Moloney leukaemia virus[248]. Particularly interesting is the finding that AAV, wh retrogradely transported efficiently to motor neurons of the spinal cord[249]. It is an efficient too factor 1 and it extends life expectancy in a murine model of motor neuron disease[249]. AAV-med paraplegin also rescued peripheral axonopathy in a model of hereditary spastic paraplegia[250]. T injections could be a method for delivering a therapeutic molecule after SCI. However, impleme research to determine the best AAV serotypes to target motor neurons efficiently, and retrograd tested in the context of SCI.

An opportunity exists for tailoring therapies to different types of injury. For example, if regener desired, knowledge of the receptors expressed on the cell body and axon will inform whether thi particular neurotrophin, and where this factor might best be applied. Similarly, there might be l that neutralizes a given inhibitory receptor if this molecule is not expressed by the axons that ar a rational basis for intervening with a given therapy by meticulously investigating the mechanis

Preclinical testing. Many preclinical therapies have not been shown to be safe and efficaciou Independent replication is extremely desirable to determine the general applicability of a therap potential therapies should be tested in models that closely approximate the human injury subty injuries in dogs, as well as surgically induced injuries in non-human primates, can be used adva response to SCI, although studied surprisingly little, has been examined after contusion injury[1 differences between rodent, cat, dog and primate nervous systems[126], many recommend that th primates for safety and efficacy[10, 11]. Despite the paucity of safety and efficacy studies using no studies and trials in humans are currently in progress[8]. This trend is of particular concern giver including transplants of stem cells or cells from the olfactory nervous system, can induce pain-r growth of sensory and sympathetic axons when tested in rodent models of SCI[72, 110, 254, 255]. nociception, autonomic dysreflexia and spasticity should therefore take place in animal models patients to ensure that therapies neither induce adverse consequences nor interfere with the nat function that can occur. For example, when transplanting cells, care should be taken not to abla trabeculae or axons spared in circumferential white matter[29, 256].

There are also relatively few studies that report outcomes after intervening more than 1 month p [258], and, of these, many fail to detect improvements in axon growth or functional recovery. This repair is to be achieved in individuals with long-standing injuries. Additionally, relatively few st functional recovery go on to determine whether these changes remain stable beyond 2 or 3 mon

Clinical trials networks. Various databases of patients with SCI have been established to fo SCI and to enlist and document patients that might be suitable for particular clinical trials. Eur trial networks have been established to be ready to implement interventions across multiple cer

standardized evaluation using clinical outcome measures, imaging and neurophysiological stim researchers and others, including the FORE-SCI groups, are developing additional tests of sens allow more sensitive assessment of recovery of function after SCI[7].

Conclusions

SCI is a devastating condition for which there is as yet no cure. Cellular, molecular and rehabilit developed and some are now in, or moving towards, clinical trials. Nevertheless, work remains t of these therapies can safely improve outcome after human SCI. To distinguish therapies that a the scientific and clinical SCI communities recommend that preclinical studies should be repro Individual therapies are unlikely to emerge as a cure for SCI. Rather, we predict that tailored co cumulative improvements in outcome after different types of SCI.

Links

FURTHER INFORMATION

- **Acorda Therapeutics**
- **American Spinal Injury Association**
- **BioAxone Therapeutic**
- **Christopher Reeve Foundation**
- **Clinical Trials.gov**
- **Foundation for Spinal Cord Injury Prevention, Care and Cure**
- **International Campaign for Cures of Spinal Cord Injury Paralysis**
- **Miami Project to Cure Paralysis (FORE-SCI)**
- **National Institute of Neurological Disorders and Stroke (NINDS) Facilities of Cord Injury**
- **Neuraxo Biopharmaceuticals**
- **NINDS workshop on translating promising strategies for spinal cord injury tl**
- **Proneuron**
- **Reeve–Irvine Research Centre, University of California, Irvine (FORE-SCI)**
- **Seikagaku Corporation**

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Competing interests statement

The authors declare **competing financial interests**.

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